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# ANNALS OF INTERNAL MEDICINE

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## SURGICAL TREATMENT OF BRONCHIECTASIS \*

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PERMANENT cure of bronchiectasis can be obtained only by pulmonary resection. The operative mortality and morbidity are today so small in contrast to that inherent in the disease that operation can be recommended without hesitation. The opinions in this report are based on the treatment of 390 patients with bronchiectasis at this Chest Center and at Percy Jones General Hospital during the past three years. During this period there have been 220 consecutive lobectomies with only one death, an incidence of 0.4 per cent. This fatality was the fourth patient to be operated upon at this hospital. One hundred and eighty-four lobectomies were performed for bronchiectasis, 20 for pulmonary cysts, 11 for chronic pulmonary suppuration, three for bronchial adenomas associated with suppuration, and two for basilar tuberculosis. The bronchiectasis in the patients not operated upon was either too minimal, too patchy and diffuse, or too extensive. A small number of patients refused operation. The bronchiectasis in five patients involved the entire lung and required pneumonectomy. The purpose of this paper is the presentation of the surgical management of patients having lobectomies, with particular reference to those having bronchiectasis. The selection of patients for operation, the preoperative, operative, and post-operative management, and complications are discussed. Pulmonary function before and after operation as determined by bronchspirometric studies in a smaller group of patients is presented.

The clinical course of patients with bronchiectasis is known to all. It is characterized by chronic sepsis, varying degrees of debility, and usually recurring attacks of pneumonia. There may be remissions with relative freedom from symptoms. This does not mean that the bronchiectasis is healed. The degree of disability is largely dependent on the degree of sepsis

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which in turn is dependent largely on the adequacy of bronchial drainage. The destructive changes in advanced bronchiectasis are permanent and irreversible.

In the development of this disease, the ciliated columnar epithelium is frequently ulcerated and replaced by non-ciliated cuboidal or squamous epithelium and the normal elastic tissue and smooth muscle fibers are partially or completely replaced by granulation or scar tissue. Because of the loss of the normal cleansing action of the bronchial tree due to the loss of the ciliary action of the mucous membrane and the peristaltic action of the bronchial wall, stasis of exudate and resulting infection occur.

The prognosis of patients with untreated or medically treated bronchiectasis is poor. Roles and Todd<sup>1</sup> reported a mortality rate of 47 per cent in the 49 non-surgical cases followed by them over a six-year period. Perry and King<sup>2</sup> followed 260 untreated or medically treated bronchiectatic patients over a 12-year period. The mortality rate for the traced males was 36 per cent, as compared to 26 per cent for females. The mortality rate as shown by them was higher when the bronchiectasis was cystic (55 per cent), or saccular (37 per cent), than when cylindrical (13 per cent). Patients having bilateral bronchiectasis had a 42 per cent mortality rate during this 12-year period in comparison to 25 per cent for unilateral cases. This illustrates the higher mortality rates in the more severe and extensive degrees of the disease.

Apart from the mortality, the morbidity is also considerable. Thirty-five per cent of the 100 patients followed by Riggins<sup>3</sup> during a 10-year period were unable to work because of the severity of their disease or psychological effects of the foul-smelling, productive cough. An additional 40 per cent worked only part time, their work being frequently interrupted by exacerbations. Many patients have suffered the effects of chronic sepsis for so long that not until after a lobectomy do they realize that it was possible to have felt better. Some patients with bronchiectasis live out their life span; one can not foretell those who will.

Conservative therapy to improve bronchial drainage, combat infection, and improve the general physical condition of the patient is of value and should be employed. Postural, as well as bronchoscopic drainage, breathing and coughing exercises, eradication of other foci of infection, high vitamin, high caloric diets, supplementary vitamin therapy, medicaments to thin viscid bronchial exudates, as well as chemotherapy, are valuable adjuncts in the management of bronchiectatic patients. Penicillin<sup>4</sup> is of value in the treatment of the recurrent pneumonic episode. It also decreases the amount of sepsis and intoxication during the interval stages. In no patient with advanced bronchiectasis, however, can the sputum be made to disappear completely. When penicillin is discontinued symptoms invariably recur in a short period of time. Penicillin in no way improves the underlying pathological changes and as such is no safeguard against exacerbation of infection and symptoms. One can temporize with the disease over a period of years

by symptomatic treatment. Even though apparent improvement results, no one denies the part played by chronic sepsis in the development of degenerative changes in the heart, liver, kidneys, and blood vessels. Death from bronchiectasis usually results from pneumonia, septicemia, pericarditis, right heart failure, hemorrhage, or empyema. The possibility of these hazards is present as long as the bronchiectasis exists. One must then decide between palliative therapy and a permanent cure.

*Selection of Patients for Operation:* Decision as to operative therapy depends upon the amount of disability, the extent of the destructive changes, and the physical evidence of chronic intoxication. It is obvious that patients with bronchographic evidence of bronchiectasis who otherwise show no significant clinical evidence of the disease do not require surgical treatment until such a time as otherwise indicated. Furthermore, patients with minimal bronchiectasis can be cared for conservatively, and those whose bronchiectasis involves all five lobes are beyond the realms of surgical treatment and must be cared for conservatively. If there are no other contraindications to operation, lobectomy is recommended.

Bronchiectasis is bilateral in approximately 30 per cent. Studies, such as the one by Perry and King, show a mortality rate as high as 42 per cent for patients with bilateral bronchiectasis during a 12-year period. The associated morbidity is even greater. In view of this, a definite attempt should be made to treat these patients. Those patients with advanced bronchiectasis on one side and minimal on the other who had lobectomies on the more extensive side were so improved by operation as to make this procedure well worth while.

Lobectomy, until recently, was largely reserved for those patients whose bronchiectasis was either primarily unilobar or unilateral. With the lowered morbidity now associated with lobectomy, the field of operability has increased to include those patients with extensive bronchiectasis on one side and minimal on the other, or with extensive bilateral bronchiectasis as long as the right upper lobe and upper aspect of the left upper lobe are free from disease, and whose cardiorespiratory reserve is adequate (figure 1). In the group having lobectomies for bronchiectasis, 36 patients had bilateral disease. In 28 one side was minimal enough not to require lobectomy, and in six bilateral lobectomies were performed. In the other two the second operation is contemplated in the near future. One patient had the right middle and lower lobes removed followed six months later by removal of the left lower lobe and lingula. The average interval between the two operations was four months.

*Preliminary Studies:* Adequate bronchograms outlining all five pulmonary lobes should be made with roentgenograms taken in the postero-anterior, right and left oblique, and lateral projections in order to ascertain with certainty the degree and distribution of the bronchiectasis present. If necessary, bronchographic examination should be repeated until this information is obtained. Careful bronchoscopic examination should be carried

out to determine from which lobes most of the exudate is escaping, the presence of an unduly acute inflammation of the bronchial mucosa, to eliminate the possibility of the bronchiectasis being secondary to bronchial occlusion due to foreign bodies or tumors and to improve bronchial drainage

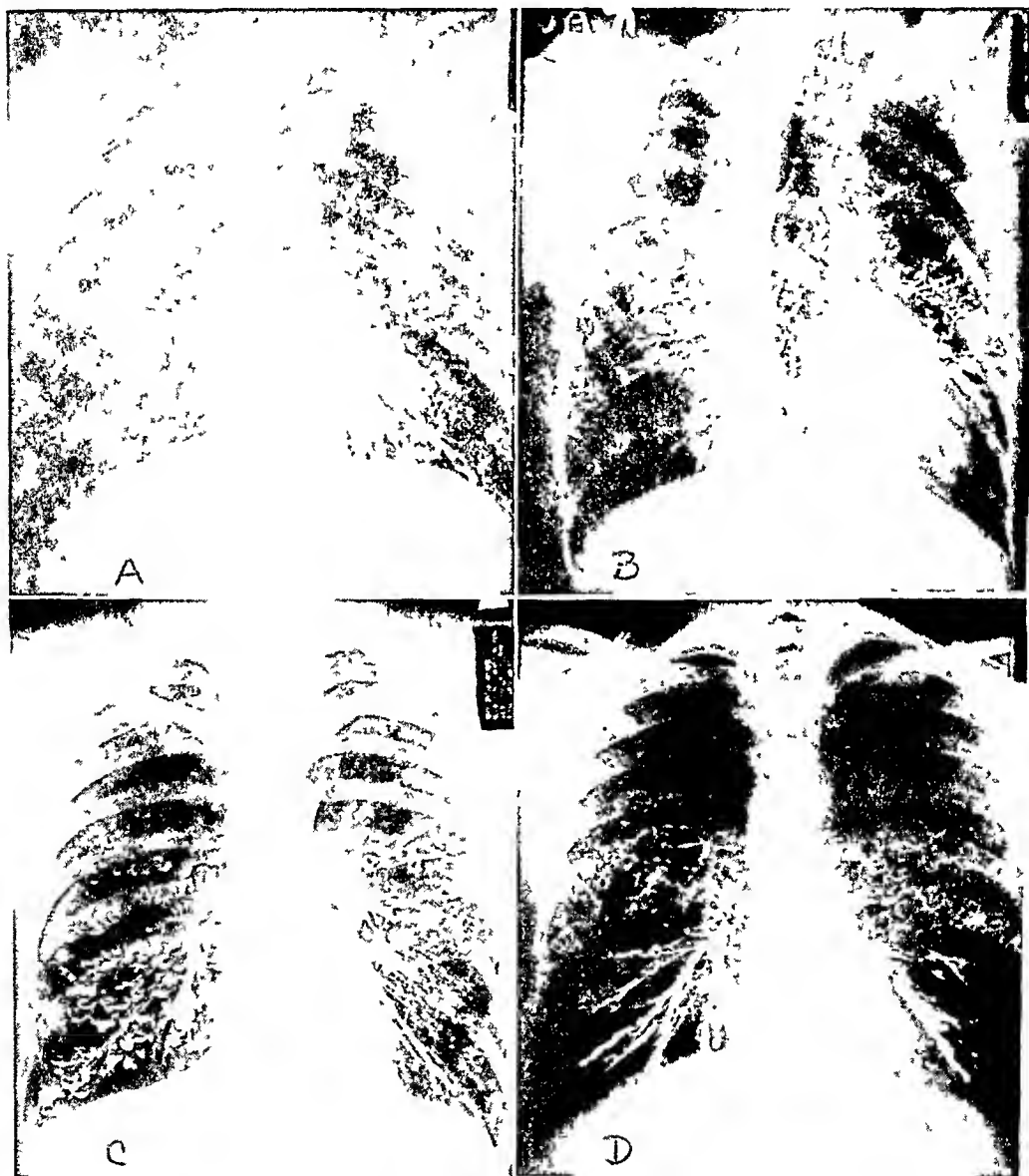


FIG. 1. Bronchograms demonstrating bronchiectasis involving the lower lobe of the left lung (A), the lower lobe and lingula of the upper lobe (B), the entire right lung (C), the lower lobes bilaterally (D).

Bronchspirometric studies to determine which is the worse side in bilateral cases, the pulmonary reserve of the uninvolved lung in dyspneic patients, or the extent of functional tissue in borderline cases have been of value in certain patients.

*Preoperative Management:* The operation should be postponed until the patient is in as good a preoperative condition as possible. A period of at least four to six weeks should elapse following the bronchographic examination to allow elimination of the iodized oil for this may cause postoperative pneumonitis. During this period of time the patient is placed on a high vitamin, high caloric diet with supplementary vitamin therapy if necessary.

The vitamin C and plasma protein components of the blood should be normal. Careful otolaryngological examination should be made and any infection so found controlled. Postural drainage should be employed three to four times daily if found effective. A one to two week course of intratracheal penicillin has been found to be of value in patients with copious amounts of sputum and with severe bronchitis. Those who have associated sinusitis are benefited by nebulized penicillin. Patients severely ill over a long period of time should have a careful medical evaluation of possible cardiac, hepatic, and renal complications and the appropriate treatment given. After the patient is so prepared, operation is performed. Intramuscular penicillin is given the evening before operation.

*Operative Technic:* No detailed discussion of the operative technic will be given. All of the operations except the first two have been done by individual ligation technic. The rôle of the anesthetist in intrathoracic operations is an important one, and his management of the anesthesia and patient determines largely the ease and safety with which the operation can be performed. The maintenance of a clear airway by efficient intratracheal and intrabronchial aspiration through an intratracheal tube of large enough caliber to allow easy aspiration and firm enough to resist collapsing is essential. The posterolateral approach with resection of the seventh rib, or the lateral approach with resection of the sixth rib has been found to give good exposure. The antero-lateral approach with resection of the fifth rib and with the head of the operating table elevated 15 to 20 degrees is of value in patients with bilateral bronchiectasis or in patients having copious amounts of sputum. This in combination with early operative occlusion of the bronchus keeps the exudate in the bronchiectatic abscesses rather than allowing it to drain out into the main bronchi to cause obstruction and perhaps aspiration into the opposite lung. Secure closure of the bronchial stump determines largely the postoperative course. The bronchus should be amputated high to prevent puddling of secretions at this site afterwards. The end of the stump is closed by over-end interrupted black silk sutures. Occasionally, two to three mattress sutures have been placed slightly proximal to this row. They are inserted longitudinally to prevent interference with the blood supply to the bronchial stump. The ends of these sutures are left long and are later used to seal down a small pleural flap developed from the mediastinal pleura directly beneath the bronchial stump. This flap is used to reinforce the bronchial closure. Silk technic is used throughout. All pleuritic adhesions between the upper lobe and chest wall are severed, for it is felt that these otherwise prevent the upper lobe from read-

justing itself to the larger space allotted to it. Closed intercostal drainage is maintained usually for 48 hours. It is essential that the thoracotomy tube is functioning properly during this period of time to allow effective drainage of the residual air and serum to insure immediate reexpansion of the remaining lobe. All patients have bronchoscopic aspiration of the intrabronchial secretions immediately postoperatively to avoid postoperative bronchial occlusion, atelectasis, and delayed reexpansion. Blood transfusions are begun at the onset of the operation and continued throughout its course; usually 1,000 to 1,500 cubic centimeters of blood suffice.

*Postoperative Management:* Adequate oxygenation is provided by means of an oxygen tent or intranasal oxygen. It has usually been possible to discontinue this after 12 to 24 hours. The maintenance of an open tracheobronchial airway is essential to early reexpansion of the remaining lobe and obliteration of the pleural space. This is accomplished by frequent intratracheal aspiration, insistence upon coughing, deep breathing exercises, and frequent change in position of the patient. Intramuscular penicillin is given for seven days in the dosage of 25,000 units every three hours. The patient routinely is gotten up by the third postoperative day. He may get up sooner in order to void, if necessary. A temporary phrenic nerve paralysis is performed during the postoperative period if the patient complains of tightness in the chest, in cases where an emphysematous lobe has been removed and over-distention of the remaining lobe is not desired, or in patients having high lingulectomies or middle lobe lobectomies in combination with the lower lobe lobectomies.

*Complications and Results:* In only one patient was significant shock from blood loss encountered. Lesser degrees of shock in other patients were only transitory and responded readily to treatment. During the postoperative period bronchopleural fistulae with resulting empyemata developed in 20 instances, an incidence of 9.7 per cent. Most of these developed during the initial phase of this series. This incidence has been reduced to 5 per cent for the last 100 lobectomies performed. Postoperative atelectasis occurred in only five instances. One of these was in the patient who had the right middle and lower lobe lobectomy followed six months later by a left lower lobe lobectomy and lingulectomy. On the third postoperative day atelectasis of the remaining portion of the left upper lobe developed that persisted in lesser degrees for the next three days. During this period of time the patient was maintained on only the right upper lobe. The intermittent use of intranasal oxygen sufficed. The lobe was completely re-aerated within three days' time with the repeated use of intratracheal aspiration. It is our opinion that postoperative pulmonary collapse is due primarily to intrabronchial exudate and occlusion. If the bronchi are kept free from secretions by frequent coughing and aspiration, this complication can be prevented. Two patients developed hemothoraces thought due to injury of the intercostal vessels at the time of insertion of the thoracotomy tubes. Six patients developed postoperative jaundice. It was difficult to

determine with certainty whether the jaundice was secondary to blood transfusions or a concomitant hepatitis, in that a number of cases of hepatitis occurred in the hospital at that time.

There was no complication from the contralateral lung in patients with bilateral bronchiectasis; however, the postoperative care and treatment in these patients was most rigid. One patient developed a postoperative cerebrovascular accident, thought probably due to a septic embolus. He was treated with both penicillin and streptomycin. A trephine was performed six weeks postoperatively and a small sterile, cystic cavity was found. This was evacuated and the patient is now well. Penicillin is given in the blood during operation to minimize the likelihood of this complication.

There was only one operative death in this series of 220 consecutive lobectomies. This was the fourth case to be operated upon at this hospital.

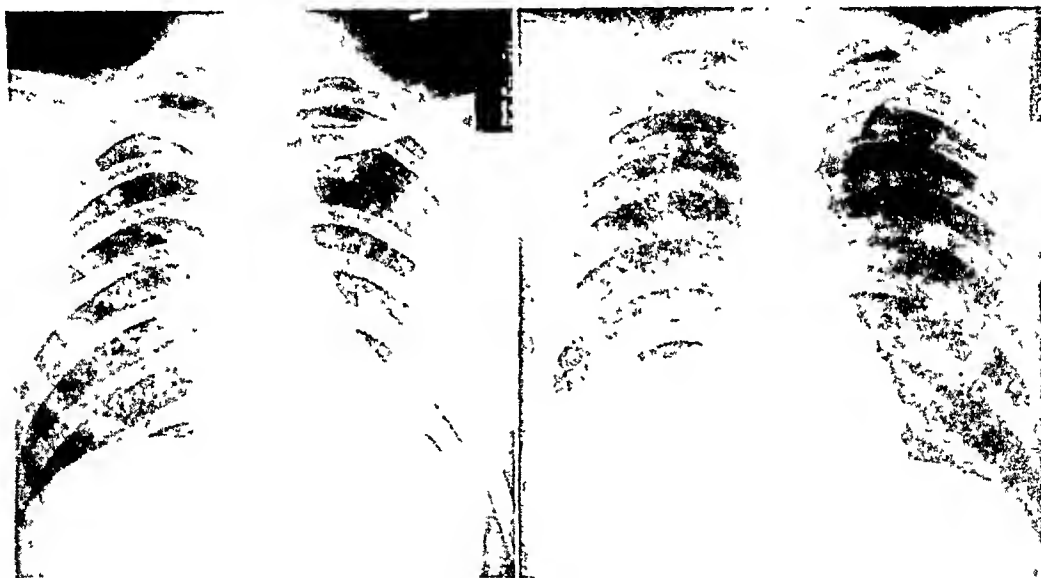


FIG. 2. (left) Roentgenogram taken 24 hours postoperatively demonstrating complete re-expansion of the remaining upper lobe. Thoracotomy tube is removed after 48 hours.

FIG. 3. (right) Postoperative roentgenogram of patient whose bronchspirometric examination is demonstrated in chart 3.

The patient died 24 hours after operation from pulmonary and cerebral edema. The operation was long and technically very difficult. A clear tracheobronchial airway and proper oxygenation were difficult to maintain during operation.

Early reëxpansion (within 24 hours) (figure 2) of the remaining pulmonary tissue concomitant with adequate drainage of the pleural space not only reduces postoperative convalescence and morbidity, but lessens postoperative pleural pain and allows better pulmonary function on the operated side as shown by bronchspirometric studies than would have been possible if any degree of pleural thickening developed.

Bronchspirometric studies performed on 26 patients postoperatively demonstrated that the pulmonary function of the remaining pulmonary tissue

on the operated side is dependent largely on the postoperative pleural complications. The objective of operative technic today is not just the removal of the pulmonary lobe, but its removal in such a manner as to be followed by an uneventful convalescence. Chart 1 demonstrates the bronchspirometric findings of a patient one month following a left lower lobe lobectomy. It illustrates the normal oxygen consumption and ventilation on the operated side in a patient whose postoperative convalescence was entirely uneventful. The operated side contributed 53 per cent of the total oxygen consumption and 52 per cent of the total ventilation. This is higher than would be expected unless some disease was present in the opposite side. Similar studies performed on a patient one year following lobectomy and another three

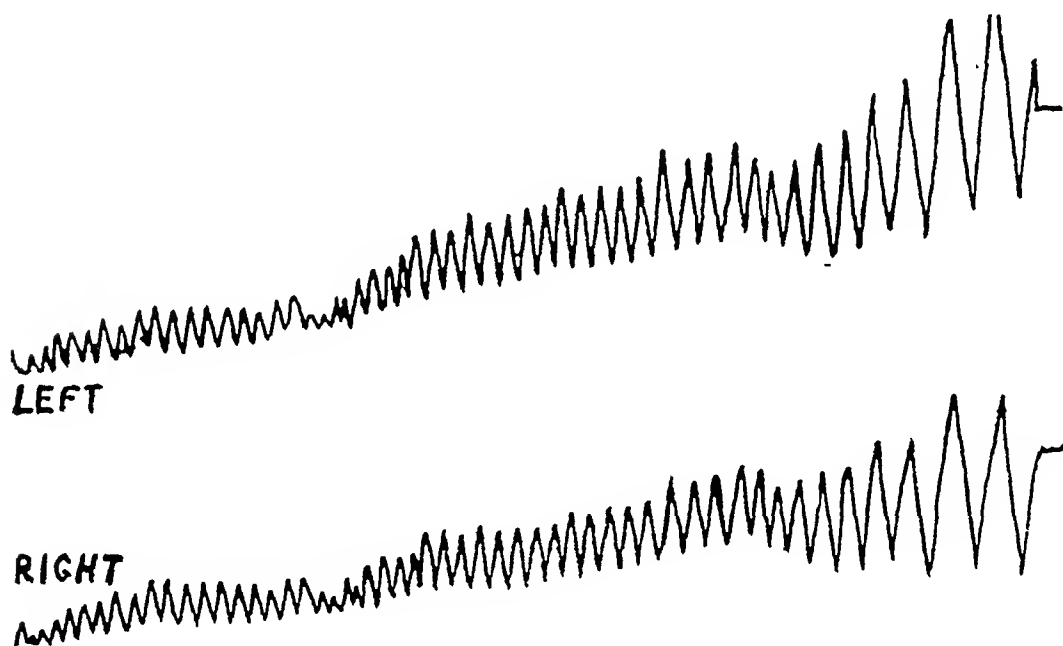


CHART I. Bronchspirometric tracing performed one month following a left lower lobe lobectomy. The operated side (left) contributed 53 per cent of the total oxygen consumption and 52 per cent of the total ventilation.

years following lobectomy showed that the pulmonary function on the operated side was almost within normal limits. Evidence of the decreased pulmonary function subsequent to pleural thickening is illustrated by chart 2. This patient with advanced bronchiectasis of the left lower lobe developed pneumonia and empyema on the right side in December 1943. Because of the persistence of a chronic productive cough following healing, bronchographic examination was performed which showed extensive bronchiectasis of the left lower lobe. A left lower lobe lobectomy was performed April 10, 1945. The patient withstood the operative procedure well, and the postoperative convalescence was entirely uneventful. Bronchspirometric examination performed seven weeks postoperatively demonstrated that the operated side contributed 76.4 per cent of the total oxygen consumption and

69 per cent of the total ventilation. If it had been appreciated by bronchspirometric examination preoperatively that the pulmonary function of the right lung was this poor, lobectomy would have been done with some trepidation. Chart 3 demonstrates the bronchspirometric tracing in a

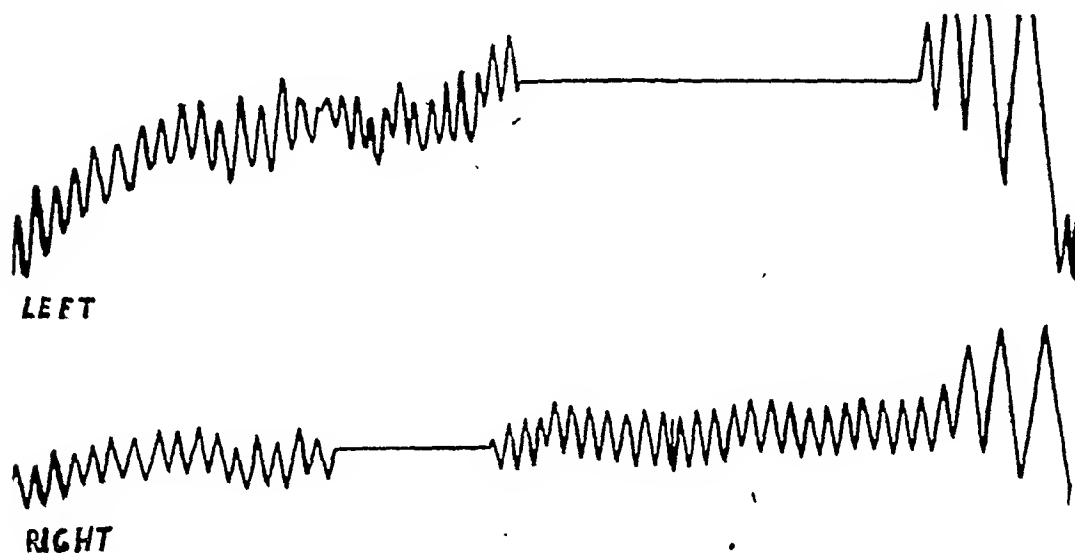


CHART II. Bronchspirometric tracing performed seven weeks following a left lower lobe lobectomy in a patient who had residual dysfunction of the right lung secondary to a pneumonia and empyema. The decreased pulmonary function secondary to the pleural thickening on this side was evident from this examination. The operated side (left) contributed 76.4 per cent of the total ventilation.

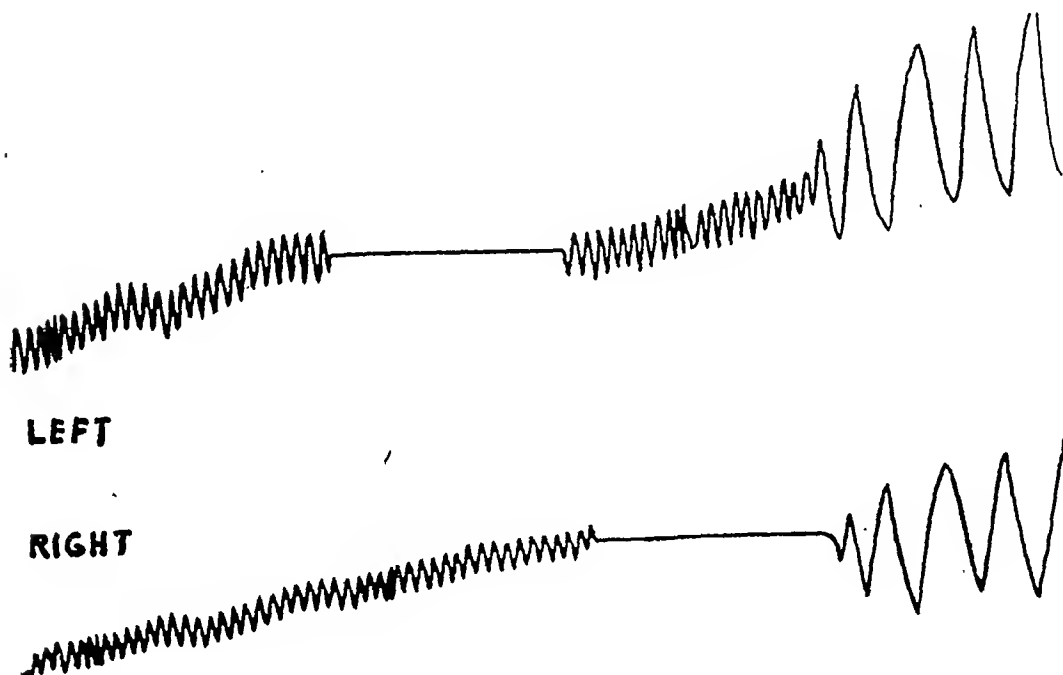


CHART III. Bronchspirometric tracing performed eight weeks following a right middle and lower lobe lobectomy. The phrenic nerve was crushed eight days postoperatively to prevent overdistention and emphysema of the upper lobe. The operated side (right) contributed 47 per cent of the total oxygen consumption and 43 per cent of the total ventilation.



patient having a right middle and lower lobe lobectomy in which the phrenic nerve was crushed during the postoperative period in order to prevent over-distention of the upper lobe (figure 3). It is noted that the function of the operated side is almost within normal limits. The right side contributed 47 per cent of the total oxygen consumption and 43 per cent of the total ventilation. In almost all cases where high lingulectomies are performed in conjunction with left lower lobe lobectomies the phrenic nerve is thoroughly crushed to prevent over-distention of the remaining segment of the upper lobe (figure 4). Chart 4 illustrates the bronchospirometric tracing in such

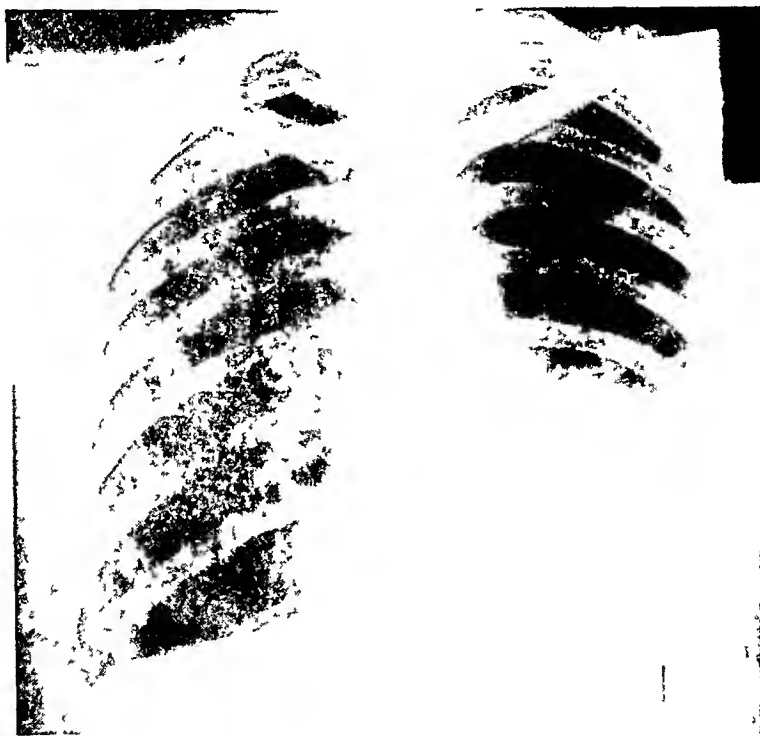


FIG 4. Postoperative roentgenogram taken seven weeks following resection of the left lower lobe and lingula of the upper lobe. The phrenic nerve was crushed three days following operation to prevent overdistention of the remaining segment of the upper lobe.

a patient. The oxygen consumption of the upper portion of the upper lobe contributed 33.3 per cent of the total oxygen consumption and 26.3 per cent of the total ventilation. This is comparable to the amount of lung tissue remaining. In cases in which the diaphragm has been paralyzed, the ventilatory factor appeared more impaired than the efficiency of oxygen absorption.

In no instance in this group was the pulmonary function following an uneventful lobectomy significantly impaired. From the above, it is shown that the pulmonary function two to three months postoperatively on the operated side in patients with uneventful convalescence may be within normal limits. Two patients upon whom lobectomies had been performed one

and three years previously also had essentially normal bronchspirometric findings. From this one might assume that the pulmonary function on the operated side following lobectomy might remain good, but a larger series of cases should have such studies performed over a longer period of time before any definite conclusions should be reached. In patients in whom an undue degree of emphysema of the residual lobe will be necessary to obliterate the residual space, elevation of the diaphragm by phrenic nerve paralysis should be accomplished to preserve the pulmonary function. If the postoperative period is complicated by bronchopleural fistulae and infection, impaired function is to be expected.

Ten patients upon whom bronchspirometric studies were performed preoperatively showed the average oxygen consumption for the bronchiectatic side to be 37 per cent of the total and the average ventilation to be 44 per cent of the total. In addition to showing the effects of bronchiectatic

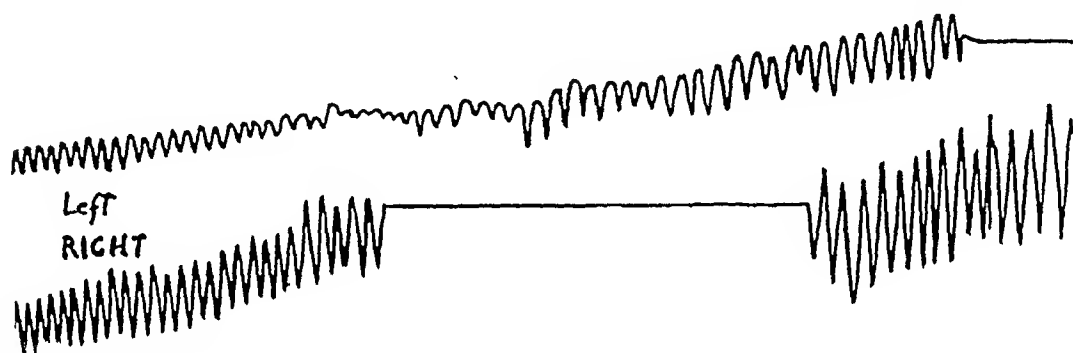


CHART IV. Bronchspirometric tracing performed seven weeks postoperatively in patient whose roentgenogram is demonstrated in figure 4. The remaining segment of the upper lobe contributed 33.3 per cent of the total oxygen consumption and 26.3 per cent of the total ventilation.

destruction on pulmonary function, this illustrates that the efficiency of oxygen absorption into the alveolar capillaries or through the alveolar membrane is more impaired than the ability to ventilate the lung. It further illustrates the inaccurate impression of pulmonary function that would be obtained from vital capacity studies alone. It is of interest to note that bronchspirometric studies performed on one patient with minimal bronchiectasis in the right lower lobe showed that this side had the better function. The oxygen consumption in the bronchiectatic side in this patient was 61.1 per cent, as compared to 38.9 per cent for the apparently good side. It is evident that in this patient destructive changes not apparent roentgenologically on bronchographically were present in the supposedly good lung. In another patient with segmental bronchiectasis of the right lower lobe, the oxygen consumption and ventilation upon that side were normal. Two patients not included in the above had such copious amounts of sputum as to cause bronchial obstruction to the extent that no oxygen absorption on the affected side took place.

From this it is apparent that the bronchiectatic lobe in many contributes very little to the oxygenation and gas exchange of by circulating its pulmonary tissue; that blood returns to the heart unox- and with a high carbon dioxide content. This in turn is largely sible for the evidence of cyanosis and dyspnea seen in these patients removing the diseased or bronchiectatic tissue, blood can then only culated through alveoli that allow the proper oxygenation and diff gases.

### SUMMARY

Permanent cure in bronchiectasis can be attained only by pulmonary resection. The operative mortality and morbidity is today so small in contrast to that inherent in the disease that operation can be recommended without hesitation. The surgical management of 220 consecutive lobectomies with only one operative death is presented, an incidence of 0.4 per cent. Postoperative bronchopleural fistulae and empyemata occurred in 10 cases, an incidence of 9.7 per cent. Pulmonary function as determined by bronchspirometric studies in a small group of patients pre- and postoperatively demonstrated that the oxygen consumption and ventilation within several months postoperatively were only slightly below preoperative values and in most cases either essentially the same or improved over operative levels.

*Note:* Since this paper was submitted for publication, 38 additional lobectomies were successfully performed.

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# LATE RESIDUALS IN PRESUMABLY CURED ACUTE INFECTIOUS HEPATITIS \*

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RECENT epidemics of acute infectious hepatitis have been the subject of intensive investigation. Interest has been largely focused on etiology, epidemiology, pathology and treatment, and many important contributions have been made. Relatively little attention has been paid to the residuals and relapses of this disease and many questions regarding its prognosis remain unanswered.

Ninety to 95 per cent of patients with infectious hepatitis apparently recover in a period of two to three months. The clinical course in the remainder varies considerably. We have had an opportunity to study a large number of patients with infectious hepatitis, most of whom have had a prolonged course. Our interest has been focused on the factors responsible for the delayed convalescence, the occurrence of late residuals and the development of relapses.<sup>1</sup> In conjunction with these studies we have investigated a large number of individuals who have had infectious hepatitis in the past and who were presumably cured. The results of this investigation are the subject of this report.

A number of investigators have reported evidence of impaired liver function in a high proportion of individuals who have recovered from acute hepatitis.<sup>2, 3, 4, 5, 6</sup> Most of these observations have been made on small groups of patients and liver function studies have been limited to a single type, usually the bilirubin excretion test<sup>2-4</sup> or the level of the serum bilirubin.<sup>5</sup> Symptoms referable to the liver have been noted by some,<sup>2, 4, 7</sup> but not by others.<sup>5, 6</sup> Although enlargement of the liver has been present in a variable proportion of most groups,<sup>2, 4, 5, 7</sup> it has not been found in all.<sup>3, 6, 8</sup> Scant attention has been paid to the possible factors responsible for the occurrence of these late residuals, and their significance remains in doubt. Although they are compatible with good health for long periods, it has been suggested that they may be a forerunner of cirrhosis.<sup>2, 3, 5, 7</sup>

The purpose of this investigation has been (1) to determine the incidence of residuals in a large group of individuals presumably recovered from acute infectious hepatitis, (2) to evaluate the factors that may have played a rôle in their occurrence, and (3) to assess their clinical significance.

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## MATERIAL AND METHODS

Approximately 3,000 patients were surveyed by questionnaire regarding a history of jaundice in the past. After excluding cases admitted because of jaundice or its sequelae and those who, on careful questioning, did not appear to have had a definite attack, there remained a total of 217 patients with a clear-cut history of acute hepatitis with jaundice in the past. The interval between the onset of the disease and the medical survey varied from two months to 27 years.

*History.* Each of these patients was interviewed and a detailed history of his attack recorded. Emphasis was placed on the depth and duration of jaundice, the duration of bed rest, the alcohol intake, the presence of syphilis or other complicating disease, the relation of the attack to transfusions of blood or plasma or to the inoculation of yellow fever vaccine, the occurrence of relapses or reinfections and the presence of symptoms.

The depth of jaundice was recorded as mild, moderate or severe. Where the icterus index was known values up to 50 were considered mild, between 50 and 100 moderate, and over 100 severe.

Patients who developed their jaundice within two to four months of a transfusion of blood or plasma or an inoculation of yellow fever vaccine were classified as homologous serum jaundice or yellow fever vaccine jaundice respectively. Since there is no conclusive evidence to indicate that the etiology and pathology of these two forms of hepatitis are different from those of infectious hepatitis, they have been included in this study, although the residuals in each group have been considered separately. One hundred and sixty-seven patients had had infectious hepatitis, 30 homologous serum jaundice, and 20 yellow fever vaccine jaundice.

Residual symptoms were considered significant only if they were moderate to severe in degree, definitely had their onset with the attack of jaundice, had been present continuously since, and could not be attributed to any other cause present.

*Physical Examination.* The abdomen was examined carefully for evidence of liver enlargement and tenderness, splenomegaly and collateral venous circulation. The sclerae were inspected for icterus and the skin for spider nevi and palmar erythema.

The liver was considered enlarged when it could be palpated at least one finger's-breadth below the right costal margin in the mid-clavicular line and when its upper border was percussed no lower than the fifth intercostal space anteriorly. The character of the edge and its consistency were recorded. Subcostal tenderness was elicited in the usual manner, percussion tenderness by striking the fist sharply against the hand placed across the lower right chest anteriorly, and compression tenderness by the method previously described.<sup>9</sup>

*Liver Function Studies.* It is generally accepted that a complete appraisal of liver function cannot be attained by any single test,<sup>10</sup> especially

when minor degrees of impairment are present. It is necessary, therefore, to study liver function by a variety of methods. In our experience a fair estimate of liver function can be made by determining the one-minute and total serum bilirubin, the thymol turbidity and cephalin-cholesterol flocculation reactions, the bromsulfalein excretion, the quantitative urinary urobilinogen excretion, and the total serum proteins and albumin-globulin ratio. Due to conditions beyond our control it was not always possible to carry out all these studies on every patient in this investigation. The number of tests performed is enumerated in table 2. The total serum proteins and albumin-globulin ratio were determined too infrequently to be included in our results.

The fasting *one-minute serum bilirubin*<sup>11</sup> was considered abnormal when it was above 0.2 mg. per cent. All our normal controls fell below this level.

The fasting *total serum bilirubin*<sup>12</sup> was considered abnormal when it was above 1.0 mg. per cent. Our normal controls usually fell below 0.75 mg. per cent.

The Maclagan *thymol turbidity test*<sup>13</sup> was considered abnormal when values of 5 or above were obtained.

The *cephalin-cholesterol flocculation test*<sup>14</sup> was considered abnormal when there was a minimum of 1 + flocculation in 24 hours and 2 + in 48 hours.

The *bromsulfalein excretion* was determined by measuring the retention of dye at the end of 45 minutes following the intravenous injection of 5 mg. per kilogram of body weight.<sup>15</sup> A retention of 6 per cent or more was considered abnormal. Normal controls rarely showed any retention. The significance of values between 1 per cent and 5 per cent will be discussed later.

The quantitative urobilinogen determination was carried out by Watson's method<sup>16</sup> on urines collected between 9 and 11 a.m. following the ingestion of 200 c.c. of water. A minimum of three specimens was studied. If two of the three specimens contained more than 1.2 units it was considered as evidence of impaired liver function. In our experience normals usually excrete less than 1.0 unit, but a few excrete between 1.0 and 1.2 units in two hours, so that we have eliminated all border-line values in this study.

*Statistical Analysis.* All data included in the tables that follow have been subjected to statistical analysis by the Chi-Square Test. Differences between groups were considered significant only when  $X^2 = 6.0 +$ ;  $n = 1$ ;  $P < 0.015$ .\*

## RESULTS

One hundred and eight of our 217 cases (50 per cent) of presumably cured infectious hepatitis had symptoms referable to the liver, hepatomegaly or evidence of impaired liver function. Forty-seven (22 per cent) had

\* The authors are indebted to Dr. Alexander W. Winkler, Yale University School of Medicine, for his assistance in analyzing our data.

symptoms, 59 (27 per cent) had hepatomegaly and 41 (19 per cent) had evidence of impaired liver function. There was considerable overlapping of these residuals, so that one-third of the patients had two or more of the three groups of residuals (table 1). There did not appear to be any significant relationship between the incidence of residuals and the time elapsed since the onset of hepatitis (tables 1 and 2).

*Symptoms.* A great variety of symptoms have been attributed to the liver with residual damage following an attack of acute hepatitis.<sup>2</sup> After careful analysis of our data we found that only two symptoms could be considered significant—fat intolerance and pain (table 2). The other symp-

TABLE I

Relation of Residual Symptoms, Hepatomegaly and Impaired Function to the Interval Since the Onset of Jaundice in 217 Cases of Presumably Cured Infectious Hepatitis

	Total Cases	Interval			
		2-4 mos.	5-12 mos.	1-4 yrs.	5-27 yrs.
<i>Hepatomegaly</i>	59 (27%)	9	16	27	7
With symptoms	12	1	5	5	1
With impaired function	7	1	2	4	0
With symptoms and impaired function	9	0	4	5	0
<i>Symptoms</i>	47 (22%)	4	26	16	1
With hepatomegaly	12	1	5	5	1
With impaired function	2	1	0	1	0
With hepatomegaly and impaired function	9	0	4	5	0
<i>Impaired Liver Function</i>	41 (19%)	6	11	18	6
With hepatomegaly	7	1	2	4	0
With symptoms	2	1	0	1	0
With hepatomegaly and symptoms	9	0	4	5	0
<i>Hepatomegaly, Symptoms or Impaired Liver Function</i>	108 (50%)	16	38	41	13

toms elicited could not be traced to the attack of jaundice and very frequently other factors played a rôle in their inception. As already indicated only moderate or severe degrees of discomfort were considered significant.

*Fat intolerance* was by far the most striking symptom and occurred in 44 of the 51 patients with symptoms. The intolerance was almost invariably limited to fried foods and pork and rarely extended to the bland fats of milk, butter and eggs. It was usually manifested by vague discomfort or pain, bloating and eructations shortly after eating.

*Pain* occurred in 18 cases. In most of these it was associated with fat intolerance and was poorly localized in the right upper quadrant and epigastrium. In the others it appeared to be related to tenderness of the liver and was precipitated by deep breathing, bending, twisting and jarring. As a rule it was aching in character and was never colicky.

Twenty-three of the 47 cases with symptoms had enlargement of the liver, evidence of impaired liver function or both (table 1).

*Physical Findings.* Significant enlargement of the liver was found in 59 of the 217 cases studied. Twenty-eight of these had associated symptoms, or impaired liver function or both (table 1). In addition, there were 34 patients with borderline enlargement of the liver. Some of these were probably significant, since they were associated with symptoms or impaired function, but they have been excluded from consideration.

Thirty-six of the 59 enlarged livers exhibited mild to moderate percussion tenderness. Subcostal and compression tenderness occurred much less fre-

TABLE II  
Residuals Found in Presumably Cured Acute Infectious Hepatitis

	Total (217 cases)	Interval Since Onset of Hepatitis			
		2-4 mos. (32 cases)	5-12 mos. (72 cases)	1-5 yrs. (81 cases)	5-27 yrs. (32 cases)
<i>Symptoms</i>					
Fat intolerance	44 (18%)	4	23	16	1
Pain	18 (8%)	1	11	6	0
<i>Physical Findings</i>					
Hepatomegaly	59 (27%)	9	16	27	7
With percussion tenderness	36	6	10	17	3
With local tenderness	16	3	4	7	2
With compression tenderness	8	1	0	5	2
Splenomegaly	7 (3%)	2	3	2	0
<i>Impaired Function</i>					
Serum bilirubin					
One minute	2 (1%)†	1 (30)*	0 (61)*	1 (66)*	0 (32)*
Total	9 (4%)†	2 (32)*	1 (72)*	4 (80)*	2 (32)*
Thymol turbidity	7 (4%)†	1 (30)*	1 (61)*	3 (57)*	2 (31)*
Cephalin-cholesterol	12 (11%)†	1 (11)*	5 (46)*	4 (42)*	2 (10)*
Bromsulfalein	15 (11%)†	2 (18)*	4 (39)*	9 (65)*	0 (20)*
Urobilinogen	17 (13%)†	4 (13)*	5 (44)*	7 (62)*	1 (15)*

\* Number of tests performed.

† Per cent of total number of tests performed.

quently (table 2). A large number of patients had percussion, subcostal or compression tenderness of mild degree without hepatomegaly. Although some of these may have been of significance, especially when there was evidence of impaired liver function, they have been excluded from consideration.

The enlarged liver usually had a sharp, soft, easily palpable edge, but in six the edge was described as round and soft, and in three as sharp and firm. The latter will be discussed later.

An enlarged spleen was palpated in seven patients. All had one or more residuals of hepatitis, including six with symptoms, five with hepatomegaly and three with impaired liver function. Although none had had attacks of malaria, four had seen service in malarious areas and had taken suppressive atabrine therapy.



One patient exhibited faint scleral icterus in association with an enlarged, non-tender liver, but his one-minute and total serum bilirubin levels were normal, so that the finding was not considered significant.

One patient with borderline enlargement of the liver had prominent veins over the abdominal wall and chest, but there was no evidence of ascites or impaired liver function.

Typical spider nevi were demonstrated on the chest of one case, but they were not considered significant because their appearance antedated the jaundice by a considerable period and there were no evidences of liver damage.

Palmar erythema was not found in any of our cases.

*Liver Function Tests.* Forty-one cases (19 per cent) had evidence of impaired liver function. In 31 of these impairment was demonstrated by two or more tests (table 3). Residual symptoms, hepatomegaly or both were present in 18 (table 1).

TABLE III

Confirmatory Evidence of Liver Damage with Tests Indicating Impaired Liver Function

	No. of Abnormal Tests	Other Abnormal Tests	Hepatomegaly	Symptoms	None
1 min. bilirubin	2	2	0	0	0
Total bilirubin	9	5	3	3	3
Thymol turbidity	7	2	1	1	4
Cephalin-cholesterol flocculation	12	4	4	4	8
Bromsulfalein	15	9	11	9	2
Urobilinogen	17	9	9	8	4

There did not appear to be any significant difference in the time intervals during which the various tests were capable of demonstrating impaired liver function (table 2) and no one test was found to be significantly superior to the others (tables 2 and 3).

In general, the degree of impaired function revealed by our tests was mild. The following are the average and range of abnormal values we found:

	Average	Range
1 minute serum bilirubin	0.54 mg. %	0.50-0.57 mg. %
Total serum bilirubin	1.32 mg. %	1.05-2.20 mg. %
Thymol turbidity	5.8	5-7
Cephalin-cholesterol flocculation	1+/2+	1+/2+-2+/3+
Bromsulfalein retention	9%	6.7-18%
Urobilinogen (2 hour)	1.73 units	1.44-2.44 units

Although we have considered bromsulfalein retention up to 6 per cent at the end of 45 minutes normal, to exclude all borderline cases in this study, a comparison of the group showing retention between 1 per cent and 6 per cent, with the one with retention over 6 per cent suggests that the former is equally significant as an index of impaired liver function (table 4).

TABLE IV

Comparison of Confirmatory Evidence of Liver Damage with Bromsulfalein Retention of 1 to 5 per cent and over 6 per cent (45 minutes, 5 mg. per kg.)

Bromsulfalein retention	No. Cases	Confirmatory Evidence of Liver Damage			
		Any Residuals*	Other Abnormal Function Tests	Hepatomegaly	Symptoms
1 to 5 per cent	37	20 (54%)	6	10	10
6 per cent and over	15	13 (87%)	10	11	8

\* Hepatomegaly, impaired liver function or symptoms.

*Factors Influencing the Occurrence of Residuals.* The duration and severity of jaundice appeared to be the only two factors which bore any relation to the incidence of residuals (table 5). The patients with severe jaundice had a significantly higher incidence of residuals than the others. The apparent influence of the duration of jaundice, however, was probably related to the fact that jaundice lasted longer when it was severe. Eleven (73 per cent) of the 15 cases with jaundice of eight or more weeks' duration, and only 32 (16 per cent) of the 201 cases of shorter duration were classified as severe.

The type of hepatitis, age, alcohol consumption and syphilis were insignificant factors in the occurrence of residuals.

In view of the recognized influence of inadequate bed rest on the occurrence of recrudescences during the convalescent stage of hepatitis<sup>17, 18</sup> an attempt was made to study its effect on the appearance of late residuals. There was no significant difference between those who had been kept in bed for the entire duration of their jaundice or longer, and those who had had bed rest for less than the duration of jaundice.

It seemed reasonable to suppose that the additive effects of multiple attacks of jaundice would increase the incidence of residuals, but there was no statistically significant difference between the groups with and without recurrences.

The nature of these recurrences was difficult to interpret. Of the 21 patients with a single recurrence, 11 had had it under two years and 10 had had it over two years following the initial attack. Five patients had had two or more recurrences at intervals between one month and 12 years. The interval between these recurrences was under two years in six and over two years in the remaining six. Obviously, then, it was impossible to differentiate relapses from reinfections. The problem became even more difficult when the type of jaundice was considered. The history suggested that three patients had had both infectious hepatitis and yellow fever vaccine jaundice, one patient infectious hepatitis and homologous serum jaundice and one patient infectious hepatitis following an arsenotoxic hepatitis. In each of these cases the interval between the attacks had been well over two years and

TABLE V

Possible Factors in the Incidence of Residuals in Presumably Cured Acute Infectious Hepatitis

	No. Cases*	Hepatomegaly, Symptoms or Impaired Function	Hepato-megaly	Symptoms	Impaired Liver Function
<i>Type of hepatitis</i>					
Infectious	167	87 (52%)	48	35	35
Homologous serum	30	13 (43%)	5	7	4
Yellow fever vaccine	20	8 (40%)	6	5	2
<i>Severity of jaundice</i>					
Mild and moderate	169	74 (44%)	36	19	24
Severe	43	32 (74%)	21	17	15
<i>Duration of jaundice</i>					
Less than 8 wks.	197	94 (48%)	50	41	33
Over 8 wks.	15	12 (80%)	7	5	6
<i>Bed rest</i>					
Less than jaundice	107	59 (55%)	31	20	22
Duration of jaundice or longer	70	35 (50%)	14	16	11
<i>Recurrences of jaundice</i>					
None	191	91 (47%)	46	35	34
One or more	26	17 (65%)	13	13	7
<i>Age</i>					
Under 35 yrs.	204	99 (49%)	55	44	37
Over 35 yrs.	13	9 (69%)	4	3	4
<i>Alcohol consumption</i>					
None or little	128	60 (47%)	30	25	24
Moderate or heavy	54	27 (50%)	17	7	8
<i>Syphilis</i>					
Syphilitics	6	1 (17%)	1	0	0
Non-syphilitics	211	107 (51%)	58	47	41
<i>Malnutrition</i>					
Prisoners of war	43	23 (53%)	10	5	9
Non-prisoners	174	85 (49%)	49	42	32
<i>Geographical†</i>					
U.S.A.	43	19 (44%)	12	5	10
E.T.O.	83	37 (45%)	17	20	9
S.W.P.	72	40 (56%)	21	14	21
Mediterranean	19	11 (58%)	8	7	2

\* Total number of cases was 217, but data were incomplete in some groups, which accounts for differences in totals noted in this column.

† Where disease was contracted. U.S.A.—includes a few cases from Hawaii and Alaska. E.T.O.—Europe, excluding Italy. S.W.P.—Islands of Southern and Central Western Pacific Ocean. Mediterranean—Italy and North Africa.

the clinical and epidemiologic history suggested reinfection rather than relapse.

In six of the 26 recurrent cases (23 per cent) and in 37 of the 186 non-recurrent cases (19 per cent) the jaundice had been severe, so that there did not appear to be any significant relationship between recurrences and the severity of jaundice.

The recent interest in dietary factors in liver injury<sup>10</sup> led us to examine this problem. Forty-three of our cases had been prisoners of war for periods of one to three years, chiefly in the Philippines and Japan. They had all suffered severe malnutrition, complicated almost invariably by beriberi and frequently by pellagra and scurvy. A comparison of this group with the non-prisoners failed to disclose any significant difference in the incidence of hepatic residuals.

To evaluate the possibility that differences in the virulence of the infecting agent might have played a rôle in determining the incidence of residuals, the cases from each of the major Theaters of Operation and the United States were compared. No significant differences were noted.

Recently it has been pointed out that atabrine, given over a long period in the suppressive treatment of malaria, may cause serious liver disease in a few susceptible individuals.<sup>30</sup> The patients from the Southwest Pacific and Mediterranean Theaters of Operation, where suppressive treatment with atabrine was routine, were compared with those from the European Theater and the United States, and no significant difference in the incidence of residuals could be demonstrated.

## DISCUSSION

One half of our 217 patients, who were considered fully recovered from acute infectious hepatitis, had residuals evidenced by symptoms, hepatomegaly, or impaired liver function, for periods ranging up to 27 years. Others<sup>8, 4, 6</sup> have found an even higher incidence of residuals and there is good reason to believe that a higher incidence would have been found in this series had a greater variety and number of liver function tests been performed. Our results have not been weighted by a large number of patients who might be considered convalescent. Only 32 in the series had had their jaundice within a four month period.

The symptoms described appeared to be related to some disturbance of the liver. In every instance they could be traced to the attack of jaundice, no other etiology could be found and in approximately one-half the patients they were associated with hepatomegaly and/or impaired liver function. Recently several workers<sup>8, 21</sup> have denied the relationship of these symptoms to liver damage and have indicated that they are psychogenic in origin. All their cases had been hospitalized for a long time and had never fully recovered, so that they can not be compared with our cases. Moreover, psychogenic factors could hardly have played a rôle in our group, since none of the patients had sought medical attention or lost time from duty because of these symptoms, even though they were moderate to severe in degree. It is noteworthy that in one of the reports<sup>21</sup> an appreciable number of the patients with psychogenic factors had hepatomegaly and impairment of liver function. Kalk,<sup>2</sup> who believes these symptoms are due to liver disease, has commented on the fact that the clinical syndrome frequently simulates psychoneurosis.

Hepatomegaly was the most common residual in our series. Our criteria for pathological enlargement of the liver were sufficiently rigid to exclude the occasional normally palpable liver in thin individuals with narrow costal angles. Moreover, the significance of our findings was enhanced by the appreciable number that were associated with tenderness and impaired function. Most other investigators<sup>2, 4, 5, 7</sup> have found hepatomegaly in an appreciable number of patients presumably cured of acute hepatitis, but have demonstrated that hepatomegaly and impaired function do not always go hand in hand,<sup>5, 21</sup> as was also true in the present investigation.

Impairment of liver function appears to be the most common residual reported in the literature,<sup>3-6</sup> whereas it was the least common in our series. This is probably related to the use of the bilirubin excretion test which is more sensitive than any of those we employed.

That the severity of the jaundice played a rôle in the occurrence of residuals was to be expected, although the relationship has not been noted by some.<sup>8</sup> We were greatly surprised, however, to find that bed rest and recurrences were insignificant factors, since in our experience with active hepatitis they proved to be very important.<sup>1</sup>

Polack<sup>7</sup> believes that inadequate treatment of an acute attack of infectious hepatitis predisposes to the development of chronic hepatitis, a syndrome not unlike those of our cases with residuals and recurrences. Our data did not permit evaluation of this possibility.

Barker,<sup>18</sup> in a recent report, has described a group of patients with persistent symptoms, signs and impaired function following an attack of acute hepatitis, who characteristically relapse when exercised. He believes these are examples of chronic active infection of the liver. None of our cases exhibited this tendency to relapse after exercise, although the clinical picture in many resembled "Chronic Infectious Hepatitis." We have, however, seen the typical syndrome in a number of our active cases with delayed convalescence.<sup>1</sup> Whether the infective agent is actually present in the liver remains to be demonstrated.

The question of whether the residuals described are due to structural changes in the liver remains unanswered, since no biopsies were performed.

There is ample evidence that impaired function may occur in the absence of gross or microscopic changes in the liver, as, for example, demonstrated by its failure to inactivate estrogen when injured by vitamin B-deficient diets.<sup>22</sup> Also, hepatomegaly in the post-hepatitis syndrome may occur in the absence of histologic changes, as illustrated by the two negative biopsies reported by Benjamin and Hoyt.<sup>21</sup> Nevertheless, periportal fibrosis, cellular infiltration, proliferation of the bile ducts and distortion of the lobules have been found in some clinically cured cases of hepatitis.<sup>23, 24</sup> How long these structural changes may persist has not been determined, although some have been demonstrated as long as four months after apparent clinical cure.<sup>21</sup> Unfortunately in neither of the recent reports on biopsy and autopsy material<sup>23, 24</sup> were data available on the status of the liver function, so that

its relation to structural changes could not be determined. In our three cases with enlarged firm livers, two of which were tender, and one of which was associated with impaired function, it seems reasonable to suppose that structural changes had occurred.

There is considerable debate over the question of whether infectious hepatitis may go on to cirrhosis. Most workers in the field agree that the vast majority of non-fatal cases go on to clinical recovery, that a variable proportion of these have residuals which are compatible with good health, but that occasionally the latter are progressive and result in cirrhosis.<sup>2, 3, 5, 7, 23</sup> Lucké<sup>24</sup> defends the view that restoration of structure is always complete, and that cirrhosis never occurs. He believes that the cases reported in which scarring was demonstrated either had it before the onset of hepatitis or suffered a form of liver disease other than infectious hepatitis.

Some of these divergent views appear to stem from differences in terminology. In the case of epidemic hepatitis presented by Dible,<sup>23</sup> which went on to what he termed "cirrhosis," there was nodular hyperplasia, bile-duct proliferation and fibrosis of the portal tracts. A number of Lucké's<sup>25</sup> fatal cases exhibited identical findings, but the appearance of the periportal areas was interpreted as dense compression of the reticulum fibers rather than fibrosis. Since he could find no diffuse scarring or evidence of progressive destruction of tissue, Lucké refused to consider the condition cirrhosis. Furthermore, in appraising his findings in non-fatal cases he failed to take into account the possibility that patients with lesions similar to those in his fatal group might survive, in which case complete restoration of parenchyma could hardly be claimed.

Whether the term "cirrhosis" should be applied to nodular hyperplasia with fibrosis, or reticulum condensation, is debatable if the rigid criteria of Karsner<sup>26</sup> are accepted. Certainly the term "coarsely nodular cirrhosis" is widely used and understood and appears to be applicable to cases like Dible's and our own.<sup>1</sup> It is difficult to prove that the fibrosis is progressive in these cases, but the clinical course has been identical with those seen in other forms of cirrhosis. Some have shown a progressive deterioration of liver function with jaundice, ascites and splenomegaly, while others have run an intermittent course with periods of remission of variable duration.

Himsworth and Glynn<sup>27</sup> have pointed out some fundamental differences in the etiology, pathogenesis and morphology of experimental portal cirrhosis and the scarring and nodular hyperplasia that supervene on the massive necrosis of the liver induced by trophic disturbances. They suggest that the massive necrosis seen in some cases of infectious hepatitis is due to trophic disturbances and that this form of necrosis always leads to scarring and nodular hyperplasia in non-fatal cases.

We have seen both nodular and portal cirrhosis following hepatitis.<sup>1</sup> In reviewing these cases, however, we found that in no instance of proved Laennec's cirrhosis could we unequivocally establish a diagnosis of acute infectious hepatitis at the onset of the disease, and in many there were features

to suggest that the cirrhosis antedated the onset of jaundice, which had been interpreted as infectious hepatitis. In the case of nodular cirrhosis, however, the clinical data and sequence of events clearly indicated that the cirrhosis was a sequel of infectious hepatitis.

In brief, then, there is evidence to support the view that infectious hepatitis occasionally leads to nodular cirrhosis, but rarely, if ever, to portal cirrhosis.

In connection with the present investigation we are faced with the question of whether the late residuals we have described may lead to cirrhosis, as suggested by some.<sup>2, 3, 5, 7, 23</sup> Our data indicate that if this occurs at all it must be rare, since no unequivocal cases of cirrhosis were discovered in the 108 cases with late residuals. There was insufficient corroborative evidence in the three cases with firm smooth livers to warrant a diagnosis of cirrhosis. Obviously a survey of this sort has the inherent weakness of dealing with a select group, from which individuals with significant defects have been excluded.

Kalk<sup>2</sup> has found the liver with the late residuals of hepatitis unusually susceptible to new toxic insults, and believes they may be responsible for the development of cirrhosis. If recurrences of jaundice may be regarded as new insults to the liver, they did play a rôle in the development of nodular cirrhosis early in the course of infectious hepatitis,<sup>1</sup> but they led neither to cirrhosis nor to an increase in residuals late in the disease. In our experience nodular cirrhosis has not developed after the first six months following an attack of acute hepatitis. It is noteworthy that of the 33 relapses in this series only seven occurred within six months of an attack of jaundice, while every recurrence in our series of nodular hyperplasia occurred in less than three months. Apparently the time element is very important in determining the susceptibility of the liver to a second injury. If sufficient time has elapsed the susceptibility may be normal, even if complete structural and functional restoration has not taken place.

#### SUMMARY AND CONCLUSIONS

1. One hundred and eight of 217 patients, who were considered fully recovered from acute infectious hepatitis, had residuals evidenced by symptoms, hepatomegaly or impaired liver function for periods ranging up to 27 years.

2. The only significant symptoms were fat intolerance and right upper quadrant pain.

3. There was evidence that these residuals indicated a disturbance of the liver, but the presence of structural changes was not established.

4. The residuals were compatible with good health and full activity over long periods of time.

5. The only factor which appeared to play a significant rôle in the incidence of residuals was the severity of the jaundice.

6. There was no conclusive evidence that the late residuals described predispose the liver to further injury by recurrent attacks of jaundice or other insults. This was in striking contrast to the findings early in the course of infectious hepatitis. The significance of the interval between the initial attack and the recurrence was stressed.

7. There was no evidence to indicate that the late residuals of infectious hepatitis progress to cirrhosis. Coarse nodular cirrhosis does occur occasionally during the first six months of chronic progressive or recurrent infectious hepatitis.

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# RESIDUAL MUSTARD GAS BRONCHITIS: EFFECTS OF PROLONGED EXPOSURE TO LOW CONCENTRATIONS OF MUSTARD GAS \*

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THE toxic effects of mustard vapor on the respiratory tract have been well known since July 1917, when the Germans first used this gas against the Allies. Gilchrist and Matz have described the residual effects in American soldiers eight to ten years after acute mustard gassing.

Less widely known is the fact that many persons employed in the handling of mustard gas and exposed to small quantities of the vapor over a prolonged period of time may sustain damage to the respiratory mucosa which may leave them partially or totally disabled. This statement is based on two and one half years of observation in the medical department of an industrial plant where over 200 patients have been treated for both the acute symptoms and the residual effects of mustard gas exposure.

Briefly, the evolution of chronic mustard bronchitis may be traced as follows:

A young white male previously engaged in farming or some other non-industrial occupation with no history of any previous chronic lung disease goes to work on the mustard filling line. There is a varying concentration of mustard vapor in the air during a good part of the working day. After a period of time ranging anywhere from three weeks to six or 12 months he begins to show signs of definite irritation of the conjunctival and respiratory mucous membranes. He develops some or all of the following symptoms: "red eyes," photophobia, lacrimation, impaired vision, blepharospasm; loss of taste and smell sensation, nose bleeds, sore throat, difficulty in swallowing, hoarseness, chest pain, retrosternal soreness, wheezing, and dyspnea. In addition there may be anorexia, vomiting, weight loss, general weakness, insomnia, and irritability. He is seen in the Out-Patient Department where he is given symptomatic treatment and perhaps several days sick leave or temporary transfer to another department. His condition improves somewhat and he returns to work in mustard only to have a recurrence or aggravation of his symptoms in several days or weeks. After a number of such episodes it becomes apparent that this man is not suitable for work in mustard and he is transferred out to another department, preferably one where he is free of contact with any toxic fumes or dust.

After removal from mustard his eyes and throat gradually heal. The conjunctivitis recedes, the vision returns to normal. The sore throat and

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hoarseness subside. The sense of taste returns but the sense of smell may remain impaired. The appetite improves. He may regain some of the weight he has lost and his general condition is better. But he is troubled by a persistent hacking cough which comes in paroxysms. It is most common in the morning but also occurs on lying down at night. It is often precipitated by physical exertion or when the man walks from a cold into a warm room or comes into contact with fumes or smoke. The cough is productive of anywhere from a teaspoonful to a cupful of white or yellow mucoid or mucopurulent sputum which may have a foul odor on occasion. There may be a troublesome wheezing and chest tightness most marked during damp weather. The patient seems to be more susceptible to respiratory infections than he was prior to exposure to mustard and the infections tend to last longer. He may note an afternoon temperature elevation of one to two degrees. Definite clinical bronchiectasis may develop as a result of repeated attacks of acute infectious bronchitis. He is hypersensitive to fumes and dust of any kind. He may develop dyspnea on slight or moderate exertion and therefore cannot perform any arduous labor.

Physical examination of the patient at this stage will usually reveal a fairly well-nourished individual who does not appear ill. Positive physical findings are confined to the chest which shows scattered wheezes and rhonchi over both lungs with occasional moist râles at the bases. Roentgenographic findings may range all the way from minimal increase in the prominence of the bronchovascular markings to definite peribronchial thickening and patchy basal pneumonitis. Lipiodol studies may show a normal bronchial tree or early bronchiectasis. Blood counts, blood serology, and urinalysis are usually negative. Repeated sputum examinations fail to reveal tubercle bacilli and usually show a predominance of gram positive cocci. The sedimentation rate is normal or slightly elevated. Vital capacity is somewhat diminished.

A few illustrative cases will clarify the picture of residual mustard bronchitis:

*Case 1.* J. T. O., 36 year old white male, construction steel worker. Past medical history is essentially negative. He first began work training painters in a mustard filling plant in August 1942. He was first treated at the Out-Patient Department in November 1942 because of red eye, sore throat, and hoarseness. His throat and larynx improved somewhat but his eyes continued to be red with excessive burning and tearing and some impairment of vision for which he was seen again several times in the Out-Patient Department in December 1942. On January 20, 1943 he was admitted to the Station Hospital with a diagnosis of mustard gas conjunctivitis, pharyngitis, laryngitis, and tracheobronchitis. His symptoms at that time were red eyes, photophobia, blurred vision, sore throat, dysphagia, cough, and chest pain. He had lost his taste sense, appetite was poor and he often vomited after coughing. He had lost 26 pounds in three months. He had frequent headaches and was very nervous and irritable. He slept little because of almost continual cough. Physical examination at this time showed scattered moist râles in both lungs. Pulse was 96; blood pressure was 122 mm. Hg systolic and 78 mm. diastolic; red blood cells 4,980,000; hemoglobin 14.4 grams; white blood cells 7,350, with a normal differential count. Roentgenograms

showed minimal increase in the bronchovascular markings, right lower lobe. Patient ran a low-grade spiking temperature between 98 and 100°, which gradually settled down to normal. He was discharged improved after 10 days in the hospital.

On July 20, 1943 he left the Arsenal. He stated that his chest was sore from almost continual coughing. Physical examination at that time revealed scattered rhonchi over the right chest. Temperature was 98.6°, pulse was 96, blood pressure was 112 mm. Hg systolic, 70 mm. diastolic. Following his resignation from the



FIG. 1. Demonstrating the limitations of ordinary chest roentgenogram in chronic chemical bronchitis. J. J. L., 30 yr. old white male, worked in mustard for 20 months. Diagnosis: chronic mustard bronchitis. Has severe productive cough, dyspnea. Physical examination showed numerous rhonchi and wheezes in both lungs, vital capacity 3000 c.c., yet plain chest film is practically normal.

Arsenal he left Alabama and went out to the northwest coast to work in construction steel. His eyes and throat cleared completely within several weeks after removal from the mustard fumes. However, he found that he continued to have a paroxysmal cough productive of about one-fourth cupful of white or yellowish mucoid sputum. The cough would often start when he became overheated or exerted himself. He found that he tired easily and finally had to leave the northwest coast because of the excessive dampness which made his chest feel tight and increased his wheezing.

He returned to Alabama in February 1945 and was hospitalized February 28, 1945 because of his persistent cough. Physical examination at this time revealed

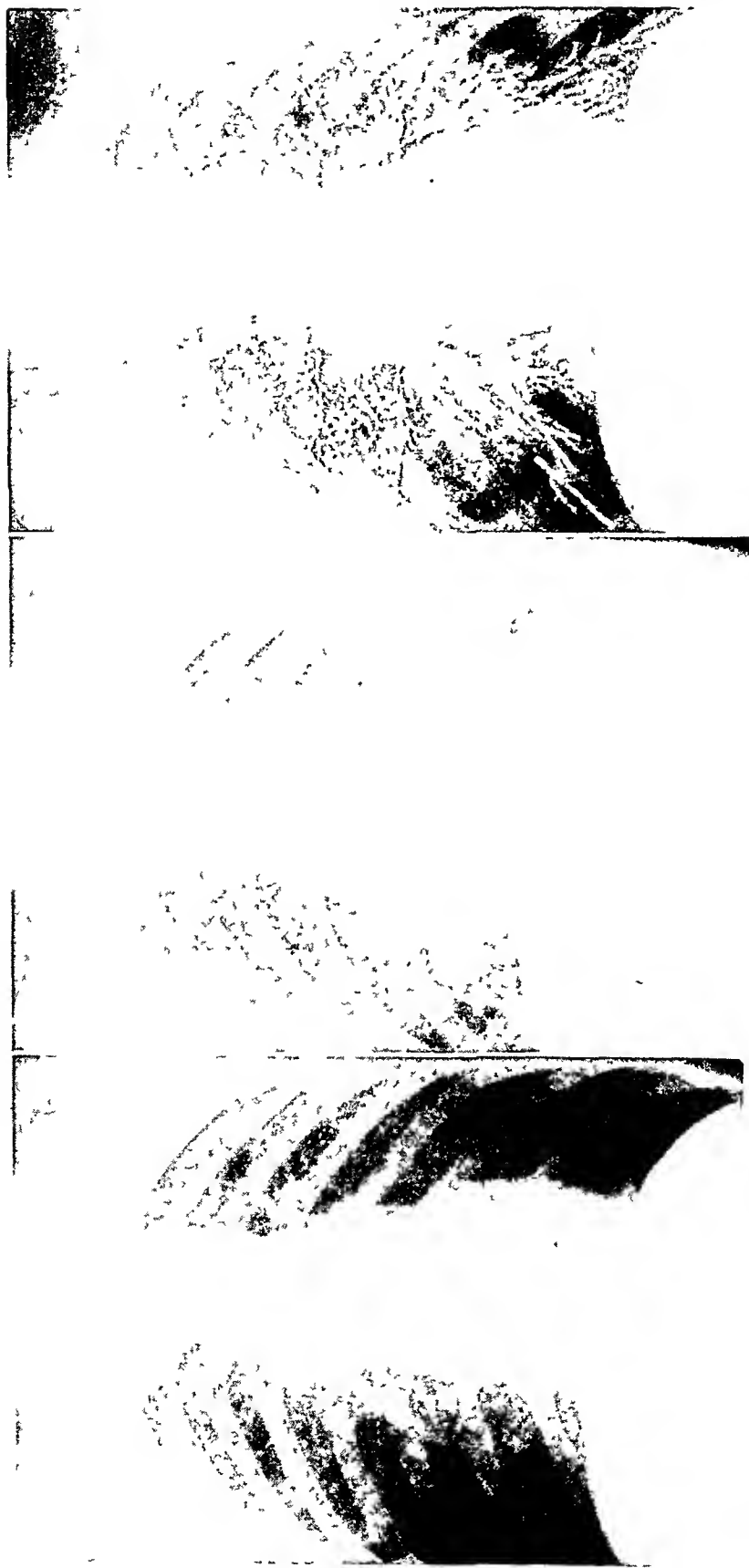


FIG. 2. J. L. C., 46 yr. old white male, worked in mustard from December 1942 to July 1943. Complained of residual cough, wheezing, and chest tightness. Film of June 15, 1943 normal except for minimal increase in the bronchovascular markings, right lower lobe. Left base is clear. Film of February 24, 1945 shows fibrosis at left base in addition to increased markings, right lower lobe. Lipiodol studies March 7, 1945 show minimal bronchiectasis, left lower lobe.

scattered rhonchi and moist râles over the entire right lung. There were a few moist râles also at the left base. Blood pressure 140 mm. Hg systolic and 80 mm. diastolic; vital capacity 3500 c.c.; sputum was negative for acid-fast bacilli and showed a predominance of gram positive cocci; urinalysis was negative; red blood cells 4,500,000; 83 per cent hemoglobin; white blood cells 9,800 with 74 per cent neutrophils, 24 per cent lymphocytes, 1 per cent monocytes, 1 per cent eosinophiles; sedimentation rate 10 mm. in one hour. Roentgenograms showed slightly increased prominence of the bronchovascular markings in the lower half of the right lung. Lipiodol studies revealed minimal fusiform bronchiectasis in the right lower lobe. Treatment consisted of postural drainage four times a day; ammonium chloride, grains 15, four times a day; high fluid intake and a high vitamin diet. His cough diminished somewhat and his sputum decreased. He was discharged home improved after 10 days in the hospital. He was seen in the Out-Patient Department on April 17, 1945, and stated that he had just been forced to quit work with a construction company because he tired too easily and could not complete the required 10-hour working day. He still has intermittent cough productive of one to three teaspoonfuls of yellowish mucoid sputum.

*Case 2.* G. C. R., a 33 year old white male; formerly worked as a farmer. Past medical history essentially negative. He was hired as an assembly operator in a mustard filling plant in August 1942. He first developed cough in October 1942. He was seen in the Out-Patient Department three times in November 1942 because of mustard gas conjunctivitis and tracheobronchitis. He was also treated several times in January 1943 because of cough, chest pain, smothering sensations, and anorexia, and he was given seven days sick leave. His symptoms persisted and he was admitted to the Station Hospital March 19, 1943. In addition to his cough which was worse at night, he also gave symptoms of paresthesia and anesthesia of the face. Physical examination on admission showed diminished breath sounds at both bases, posteriorly, with inconstant coarse râles and wheezes at the right base. Blood pressure was 96 mm. Hg systolic and 60 mm. diastolic; pulse 92; temperature 99.4°; urinalysis and test for syphilis were negative. On symptomatic treatment patient's temperature dropped to normal. After several days the cough lessened. He was discharged back to work on April 2, 1943 at which time he had only a few inconstant râles at the right base. A roentgenogram at this time showed slight peribronchial thickening at the basal portion of the left lung.

On April 23, 1943 he was seen again in the Out-Patient Department. He stated that he had gained a few pounds in weight but he still had cough productive of considerable amounts of yellow sputum. On May 10, 1943 he was again hospitalized because of cough productive of about one teaspoonful of yellowish white mucoid sputum. He had also had dyspnea on moderate exertion, tight sensation in chest, worse in cloudy or damp weather, and night sweats. His temperature was normal. Physical examination showed coarse râles at both bases, more marked on the right side. Red blood cells were 4,350,000; hemoglobin 75 per cent; white blood cells 12,450 with 82 per cent neutrophils, 14 per cent lymphocytes, and 4 per cent eosinophiles. Urinalysis was negative. Patient was treated symptomatically and was discharged, improved, on May 20, 1943. He was granted one month's sick leave. He was seen again in the Out-Patient Department on June 21, 1943, at which time he complained of his cough having been worse in the past two weeks. He claimed that he raised small amounts of foul yellowish sputum particularly in the morning. He also had anorexia, morning nausea, weakness, paroxysmal cough, and substernal soreness. Physical examination revealed fine and coarse râles throughout both lungs. Sedimentation rate was 28 mm.

He was sent to a veteran's hospital on August 5, 1943, for evaluation of his chest conditions, but he refused to stay for adequate examination. He returned to work taking lids off boxes in October 1943. He continued to work in the box factory until

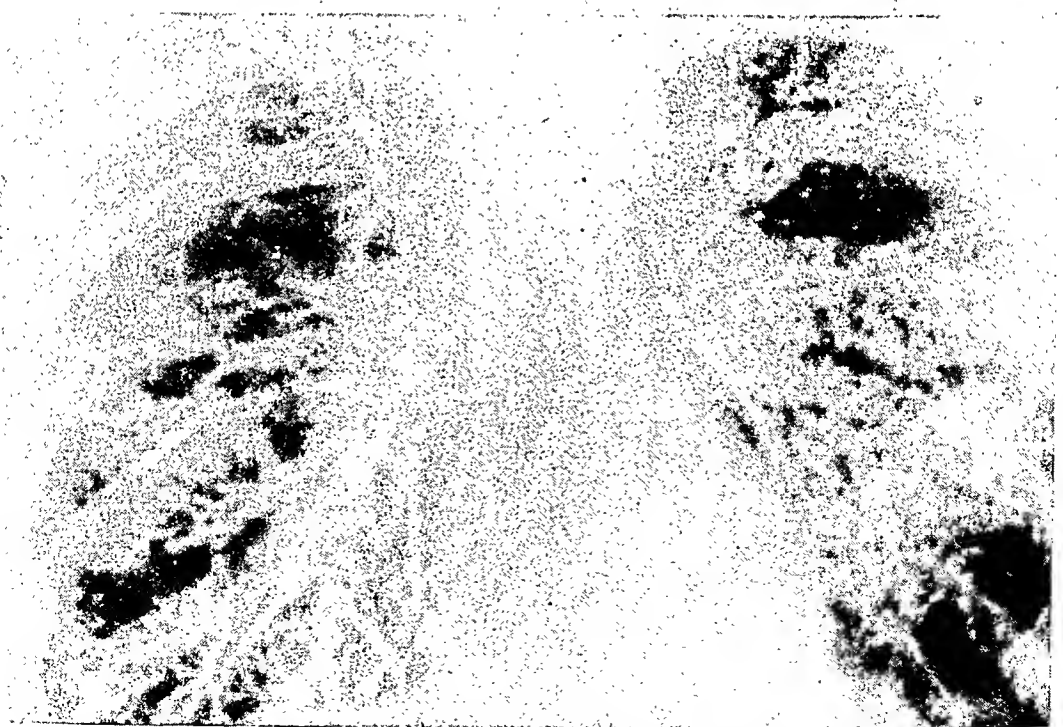


FIG. 3. J. S. B., 41 yr. old white male, worked in mustard 16 months. Complained of cough, easy fatigue, and dyspnea. Roentgenogram shows increased fibrosis at the right lower lobe. Lipiodol studies show minimal bronchiectatic changes in medial segment of right lower lobe.

May 1944, when he had to stop because of severe cough with occasional blood-streaked sputum and general weakness and nervousness. He was hospitalized at a U. S. Marine Hospital in July 1944, at which time physical examination showed many expiratory rhonchi and wheezes together with inconstant moist râles in the right base. There were also a few coarse râles in the left axilla. Sedimentation rate was 13 mm. in one hour. The diagnosis was chronic bronchitis with possible bronchiectasis. He was advised to take postural drainage, ammonium chloride, and to return to light work. Work trial, however, was unsatisfactory and he was returned to compensation status in August 1944, on which he has been ever since. Lipiodol studies done on January 25, 1945, showed no definite evidence of bronchiectasis. His vital capacity was 4800 c.c.

The patient's outstanding symptoms at the present time are weakness on mild exertion and paroxysmal cough precipitated by exertion and change of temperature.

*Case 3.* C. R. B., First Lieutenant, Chemical Warfare Service, age 30. Past history included pneumonia at the age of four with no sequelae. He had scarlet fever at the age of 13. There was no history of any chronic cough. Family history was negative for tuberculosis. He was apparently in good health until February 1943, when he was assigned to a mustard filling plant. He began to have hoarseness and developed complete aphonia several times. His eyes became red, his vision dropped from 20/30 on entrance into the Army to 20/50 in May 1943. At times his vision was so blurred that he could hardly read the headlines in the newspapers. He developed a hacking non-productive cough and had wheezes and chest pain. He remained in the mustard filling plant until June 3, 1943, at which time he was hospitalized for 10 days with a diagnosis of severe, acute, bilateral kerato-conjunctivitis, and moderately acute tracheobronchitis due to mustard. His temperature was 99.4° on admission and dropped to normal after three days. Red blood cells were 4,450,000, hemoglobin 80 per cent; white blood cells 8,150 with 76 per cent neutrophils, 24 per cent lymphocytes.

After discharge from the hospital he was transferred to the phosphorus manufacturing plant. Following his transfer his vision improved and is now back to normal. His sore throat and hoarseness subsided. From June to September 1943, his sense of taste was definitely impaired but it has gradually returned. He gained about 10 pounds in weight. He continued, however, to have persistent cough precipitated by exertion. It was productive of about two tablespoonfuls of yellowish white sputum. He also had tightness of his chest and dyspnea. In July 1944, he was hospitalized for three weeks with a diagnosis of influenza. Physical examination then showed a few rhonchi in both lungs. The blood count and urinalysis were essentially negative. A roentgenogram showed slightly increased prominence of the bronchovascular markings in the right lower lobe and also in the left mid-lung field, but no definite infiltration. His temperature was 100° on admission and gradually settled down to normal. In August 1944, he was again hospitalized because of cough, chest pain, and temperature of 103°. Physical examination at this time revealed moist râles in the left lower lobe with wheezes and rhonchi throughout the chest. A roentgenogram showed a patchy pneumonitis at the extreme left base. He was treated with sulfadiazine and his temperature dropped to normal after 36 hours. He was discharged after 11 days in the hospital.

Since that time the patient has had intermittent wheezes and chest tightness. He gets dyspneic on moderate exertion. He is very susceptible to upper respiratory infections which tend to "hang on." He gets frequent paroxysmal cough. Roentgen studies on February 16, 1945, showed definite peribronchial thickening at the left base. There was also slightly increased prominence of the bronchovascular markings in the right lower lobe. Vital capacity at this time was 3900 c.c. (87 per cent of normal). Lipiodol studies on April 12, 1943, showed minimal bronchiectasis of the left lower lobe.



*Case 4.* J. L. C., 46 year old white male formerly engaged in farming. He was hired as an assembly operator in the mustard filling plant in December 1942. On January 25, 1943, he was seen in the Out-Patient Department complaining of burning sensations in the eyes, cough, chest pain, and vomiting of blood for two days. Physical examination showed considerable injection of the conjunctival vessels, pharynx was diffusely red, and a few scattered wheezes were audible over both lungs. Temperature was 100°. The diagnosis was bilateral conjunctivitis, pharyngitis, and tracheobronchitis due to mustard gas. He was given five days accident leave. His condition improved and he returned to work. He was treated again in the Out-Patient Department on February 3, 1943, for mustard gas conjunctivitis and tracheobronchitis. On May 22, 1943, he was seen again in the Out-Patient Department at which time his chief complaint was cough. The lungs were clear at this time and the temperature was normal. On June 15, 1943, he again visited the Out-Patient Department. He was complaining of cough, weight loss, and poor appetite. A roentgenogram showed slightly increased prominence of the bronchovascular markings in the lower half of the right lung field. Sputum was negative for tubercle bacilli. On July 13, 1943, he complained of left chest pain in addition to his productive cough. Physical examination showed large rhonchi and musical wheezes over both lungs. Roentgen studies showed definite peribronchial thickening at the left base. The right lung was unchanged since the previous examination. A permanent transfer out of mustard gas was advised at this time.

On March 28, 1944, he was seen again because of cough and tightness in his chest which he claimed was caused by exposure to the colored smoke in which he worked. Physical examination revealed numerous wheezes and rhonchi over both lungs. A roentgenogram showed some clearing in the left base since the previous examination and there was definite peribronchial thickening at the right base. Permanent transfer out of exposure to all types of dust and fumes was advised. On March 7, 1945, he was hospitalized because of persistent cough, wheezing, and chest tightness. Lipiodol studies at this time showed minimal cylindrical bronchiectasis in the left lower lobe. The patient stated that his chest felt much clearer after the lipiodol studies. He was discharged to light duty.

*Case 5.* W. T. W., 24 year old white male, formerly worked in a Civilian Conservation Corps camp and did farming. Past medical history includes mild influenza in 1936, from which he apparently made a complete recovery without any residual cough. He began work in the mustard filling plant on February 8, 1943. His job was to clean up the mustard from the floor after spills or leaks. In April 1943, he developed red eyes, hoarseness, and severe cough. He could not eat or sleep because of his persistent coughing. He was treated in the Out-Patient Department and was given several days sick leave on three occasions when his symptoms became particularly severe.

In February 1944, he was transferred to another department and his symptoms began to improve. His cough and wheezing, however, persisted. He was granted a furlough in June 1944, for induction into the Army but was rejected by the Army doctors (presumably because of his chest findings). He was seen by an allergist who found sensitivity to several proteins but attempted desensitization produced no improvement in the cough. In October 1944, he was seen at the Marine Hospital where physical examination revealed some wheezes and moist râles over both lung fields posteriorly. Sedimentation rate was 7 mm. in one hour. Blood counts were normal. Sputum examination for tubercle bacilli and blood test for syphilis were negative. Lipiodol studies at that time showed no evidence of bronchiectasis. The diagnosis was chronic bronchitis due to poison gas. He was rated as having no disability at that time but was advised to avoid chemical fumes, and to have reexamination after an interval of four months. In November 1944, he was rehired at the Arsenal. On March 19, 1945, he was again seen in the Out-Patient Department. He still had a

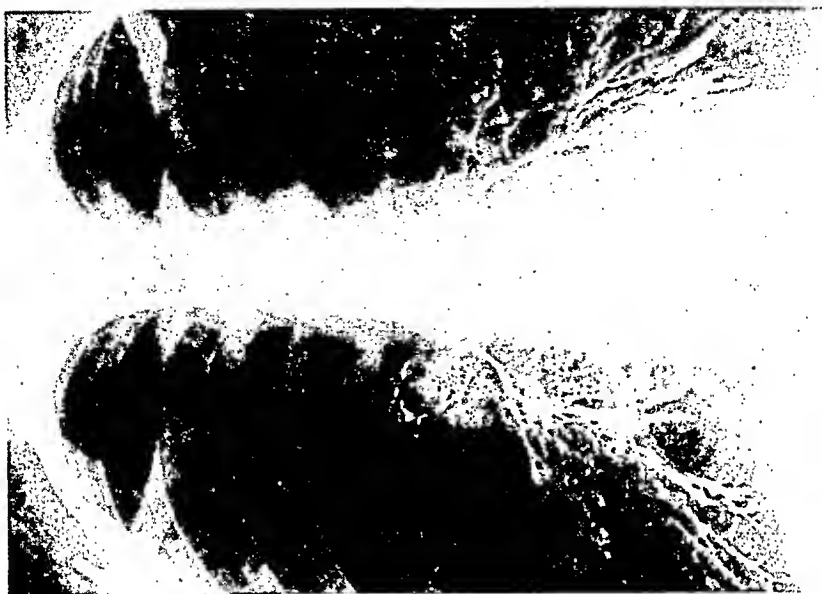


FIG. 4. L. S. M., 28 yr. old white male, worked in mustard 12 months. Has residual cough and foul sputum. December, 6, 1943, definite peribronchial infiltration at left base (? atelectasis). July 10, 1944, considerable resolution of densities noted in previous film. January 3, 1945, lipiodol studies show bronchiectasis left lower lobe.

moderately productive cough, worse on exertion and during change of weather. He stated that he raised about one half teacup of mucoid yellow or white sputum which occasionally had a foul odor in the morning but was never blood streaked. His appetite was fair. He had a wheezing and constant substernal soreness on deep inspiration. Physical examination revealed a few wheezes and rhonchi over the lower half of the left chest audible on deep inspiration. His vital capacity was 5000 c.c.

Although this man had numerous râles and wheezes in both lungs on many examinations, his chest films at no time showed any very definite changes, the findings being limited to slightly increased prominence of the bronchovascular markings in both lower lobes.

*Case 6.* D. G. M., 42 year old white male formerly engaged in farming. Gave no history of any previous chronic lung disease. Began work at the Arsenal in September 1942, and spent 10 months in the mustard filling plant. He had repeated exposure to mustard gas fumes in the winter of 1942, and spring of 1943. He was seen in the Out-Patient Department on numerous occasions and was treated for several mustard burns of the skin as well as mustard vapor conjunctivitis, pharyngitis, and tracheobronchitis. In June 1943, he complained of hoarseness, headache, and severe cough. He had lost 35 pounds in five months. A roentgenogram of the chest showed peribronchial infiltration in the basal portions of both lung fields with obliteration of the costophrenic angle, bilaterally. He was transferred out of mustard filling to another department. Within two months his eyes and throat symptoms subsided but he had a persistent residual cough frequently productive of yellowish white mucopurulent sputum. He also had irregular afternoon fever and dyspnea on slight exertion.

On May 1, 1944, he quit work because of his cough, chest pain, and dyspnea on mild exertion. On June 12, 1944, he developed an extensive pneumonitis of the right mid-lung field. In August 1944, he was seen at a U. S. Marine Hospital where physical examination showed moist râles at both bases. Pulse rate was 90 to 110; sedimentation rate was 26 mm. in one hour. Sputum was negative for tubercle bacilli; blood counts were normal. Roentgenogram at this time showed clearing of the pneumonitis in the right mid-lung field but there was evidence of peribronchial fibrosis in both bases. He was adjudged to be completely disabled temporarily and was advised to take postural drainage, ammonium chloride, and rest. He was seen again at the Marine Hospital on January 31, 1945. He had not worked for the preceding four months. He still complained of cough productive of one cupful of yellow sputum daily. He also had dyspnea and intermittent left chest pain. He stated that he had been taking his postural drainage regularly and had gained about nine pounds in weight. Physical examination showed occasional moist râles over both bases posteriorly. Blood pressure was 112 mm. Hg systolic and 74 diastolic; red blood cells were 4,650,000; hemoglobin 78 per cent; white blood cells 12,550 with a normal differential count; sedimentation rate was 26 mm. in one hour. Lipiodol studies showed extensive bronchiectasis involving the right middle and right lower lobes and also the left lower lobe. The opinion of the chest consultant was that he should be considered disabled for three months and then should be rechecked. In the meantime he was to continue his ammonium chloride and postural drainage.

*Case 7.* R. H. W., 29 year old white male formerly engaged in farming. No history of any previous chronic lung disease. He began work in the mustard filling department on the Arsenal in November 1942. After exposure to mustard fumes for about three months he began to cough and had a burning sensation of the eyes. He worked in the mustard filling department for 11 months and was then transferred to another department. His eyes have returned to normal but his cough has gradually become worse and is productive of about one tablespoonful of thick white phlegm per day. His cough is worse in the morning. He has chest pain and becomes weak and tired easily. He has never had hemoptysis, fever, chills, or night sweats.

He was examined at a Marine Hospital October 26, 1944, at which time his chest was clear. Blood pressure 142 mm. Hg systolic and 96 mm. diastolic; sedimentation rate 5 mm. in one hour; blood test for syphilis negative; red blood cells 5,500,000; hemoglobin 88 per cent; white blood cells 7,150 with a normal differential count. Lipiodol studies showed no evidence of bronchiectasis. Serial roentgenograms of the chest from January 1943, through September 1944, have been practically normal except for minimal accentuation of the bronchovascular markings in the right lower lobe.

*Case 8.* E. P., 28 year old white male. No history of previous chronic lung disease. He was exposed to mustard fumes for eight months, beginning December 1942. After three months he developed sore throat, chest pain, hoarseness, redness of both eyes, and impaired vision. He had to stay away from work on numerous occasions for several days at a time. He was finally transferred to another department. His eye symptoms subsided but his cough persisted. He also had tightness of the chest, wheezing, and undue fatigue on moderate exertion. He was studied at the Marine Hospital in September 1944, where physical examination showed inspiratory and expiratory wheezes over both lungs with coarse moist râles at both bases. Blood pressure was 124 mm. Hg systolic and 86 mm. diastolic; pulse 76; blood counts normal; sedimentation rate 3 mm. in one hour. Repeated sputum examinations were negative for tubercle bacilli. A roentgenogram showed increased prominence of the bronchovascular markings in both lower lobes and lipiodol studies showed minimal bronchiectasis in the right lower lobe. He was rated as 25 per cent disabled and was placed on postural drainage and ammonium chloride therapy.

He was reexamined at Marine Hospital in November 1944, and stated that he had gained seven pounds but he still coughed in the morning and raised about a teaspoonful of white phlegm. Physical examination of the chest at that time was essentially negative and the opinion was that he could return to light work, that he should have no disability and that he was to be rechecked in six months. Postural drainage and ammonium chloride were to be continued. He was admitted again to the Station Hospital for five days in December 1944, because of an acute bronchitis superimposed on his chronic bronchitis. His temperature at that time was 99.2°, and loud rhonchi could be heard throughout both lungs. He was discharged on December 23, 1944. He was examined at weekly intervals in January 1945, at which time numerous rhonchi and wheezes could be heard in both lungs. His vital capacity was 4600 c.c. He was tried on a light job but had to stop at the end of five days because of persistent cough. He was then given a 30 day medical furlough. He returned to a light job on March 9, 1945. At present his residual symptoms consist of wheezing and paroxysmal cough on exertion. His appetite is good.

*Case 9.* J. L. B., 29 year old white female. She had malaria at the age of 18 but has no history of any previous lung disease. From January to June 1943, she worked in the mustard filling plant as a supervisor. She had to be around small spills quite often and could not wear her mask at times. She was treated in the Out-Patient Department several times for mustard tracheobronchitis, and conjunctivitis. Following transfer out of the mustard filling plant her cough became less but still persists. It is productive of about one fourth cupful of white mucoid sputum. Cough is worse at night. Fumes and smoke will often precipitate a coughing spell. She has occasional wheezing but no dyspnea and she states that she can do a day's work fairly well. Her vital capacity is 3700 c.c. Physical examination reveals a few moist râles at the extreme right base. Roentgenogram of the chest in July 1943, showed slightly increased prominence of the bronchovascular markings, right lower lobe. Follow-up roentgenogram on March 29, 1945, showed no essential change in the findings. Lipiodol studies have not been done.

*Case 10.* W. R. S., 30 year old white male formerly engaged in farming. Past history is negative except for influenza at the age of 26. Apparently this cleared

without residual damage. He worked in mustard for about seven months beginning November 1942. He developed symptoms of mustard vapor conjunctivitis three weeks after he was hired. He was seen on numerous occasions in the Out-Patient Department from November 1942, to June 1943, primarily for conjunctivitis and severe tracheobronchitis. He expectorated blood on several occasions.

He was not seen again at the hospital until March 29, 1945, at which time he complained of cough productive of about one-half cupful of yellow mucoid sputum which was occasionally foul but not blood streaked. He had undue dyspnea on exertion, chest tightness, and wheezing. Cough was worse at night on lying down and he often was unable to sleep until he could get rid of his mucus. He had frequent paroxysms of cough when he became overheated. He also stated that he was very nervous and had frequent afternoon temperature elevation. His appetite was fair; his weight was stationary. Physical examination at that time showed numerous wheezes and rhonchi throughout both lungs, more marked on the right side with many moist râles at the right base. Vital capacity was 2800 c.c. Roentgen studies of the chest showed increased bronchovascular markings in the right lower lobe. Lipiodol studies revealed minimal bronchiectasis in the medial branches of the right lower lobe bronchus.

### DISCUSSION

Mustard vapor, like other irritant gases, produces an inflammatory reaction in the mucosa of the respiratory tract. The severity of the inflammatory process will vary with the concentration of the gas, the length of exposure, and the susceptibility of the individual. But, although the inflammation is most severe in the upper respiratory tract, decreasing in intensity downward, it is the smaller bronchi and bronchioles which tend to develop residual pathologic changes due to the accumulation of secondarily infected secretions and necrotic tissues. "The peribronchial thickening" often noted in the basal portions of the lung fields on roentgenograms may well represent small areas of patchy atelectasis. The stage is then set for the development of bronchiectasis.

Fifty-five out of 85 patients on whom lipiodol studies have been done here and at the Marine Hospital, Memphis, showed definite evidence of bronchiectasis ranging from minimal involvement of a few bronchi in one lower lobe to extensive involvement of as many as four lobes.

It must be emphasized at this point that, although the roentgenogram is of extreme importance in the study of most chest diseases, its value is definitely limited in chronic mustard gas bronchitis. A patient may have negative bronchograms and an apparently normal chest film and yet he may be partially disabled because of a persistent paroxysmal cough. Roentgen studies can show us structural changes when they exceed a certain degree but they cannot demonstrate disturbed physiology of the bronchial musculature and mucosa.

Physical findings in a patient with chronic mustard bronchitis are usually confined to the chest which shows scattered wheezes and rhonchi with occasional moist râles at one or both bases on deep inspiration or after coughing. However, even a well established case of bronchitis may occasionally sound normal on auscultation. The physician should not be misled by the

scarcity of the chest findings on a single examination. Such factors as the dampness of the weather, the type of medication used, and the thoroughness of the preceding postural drainage will influence the amount of secretions in the bronchial tree which in turn largely determine the presence or absence of adventitious sounds in the lungs.

The vital capacity of the chronic mustard bronchitis case is usually diminished. However, even this is not a completely reliable index of a man's disability. One of our patients had a vital capacity of 4800 c.c. (102 per cent of normal for a man of his size), yet he could not hold down any job because moderate exertion would usually precipitate a severe coughing spell which left him in a cold sweat, weak, and trembling.

Our present routine treatment of chronic mustard bronchitis consists of postural drainage, high fluid intake, 60 grains of ammonium chloride daily, and removal of the patient from all contact with smoke, fumes, or dust. Steam inhalations are often of value in easing the tight sensation and wheezing in the chest. An occasional dose of codeine may be indicated for relief of a harassing non-productive cough that is exhausting the patient, but its prolonged use is harmful since it inhibits drainage of the bronchial secretions.

Most patients feel considerable relief of wheezing and chest tightness for several days or weeks after a lipiodol instillation. In fact many of them refer to it as the "oil treatment."

Barach et al.<sup>5</sup> in New York, and Olsen<sup>6</sup> at the Mayo Clinic, have recently reported good results with the use of nebulized penicillin (penicillin aerosol) in cases of chronic bronchitis and bronchiectasis. Arrangements are being made for a therapeutic trial of penicillin nebulin on some of our patients.

On theoretical grounds the removal of patients to a dryer climate should be helpful.

#### SUMMARY

1. Many persons employed in the handling of mustard gas and exposed to small quantities of the vapor over a long period of time will develop a residual chronic bronchitis which may go on to bronchiectasis.

2. Many of these patients are partially or totally disabled because of a persistent paroxysmal cough on moderate exertion.

3. History and clinical findings are most important in the diagnosis of chronic mustard bronchitis. Roentgen studies may be of little value unless definite bronchiectasis can be demonstrated on lipiodol studies.

4. Treatment consists of postural drainage, high fluid intake, and 60 grains of ammonium chloride daily. Patients should be removed from any contact with smoke, fumes, or dust. Nebulized penicillin is under therapeutic trial at the present time.

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# COMPARISON OF THE CLINICAL USE OF PROTAMINE ZINC INSULIN AND GLOBIN INSULIN IN EQUAL DOSES \*

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It is generally thought now that the use of a long-acting insulin alone or mixed with unmodified insulin is preferable to the use of unmodified insulin alone in the control of patients who require insulin in addition to a measured diet. At the present time, however, there is confusion regarding the best preparation or combination of insulins for routine use. Inasmuch as most diabetics are treated by general practitioners or internists who do not specialize in the treatment of diabetic patients it is important that the treatment of diabetic patients should not become too complicated and should still be adequate. We have become interested in this problem and for about two years have undertaken an investigation of the relative merits of the use of globin insulin and protamine zinc insulin in equal doses. Recently we have been selecting the relatively few patients for treatment with combinations of protamine zinc insulin and unmodified insulin who have not been adequately controlled on either globin insulin or protamine zinc insulin. The present report is concerned only with our investigation of the relative merits of the use of protamine zinc insulin and globin insulin with zinc.

As a basis for the investigation we have assumed that diabetic patients are not well controlled unless their measured diet is close to normal in composition when sugar is omitted, unless they rarely excrete more than five grams of dextrose in the urine each day, and unless their blood sugar is not over 175 mg. per cent when it is determined before each meal, one hour after each meal and at 11:00 p.m. We have made these seven blood sugar determinations on each of two and usually more days in each case as a part of this study, but we are not advocating this number of blood sugar determinations in a day for routine use. Moderately good or adequate control, especially in older arteriosclerotic persons, probably exists if the insulin given prevents blood sugar levels higher than 200 mg. per cent and if hypoglycemia is prevented.

Our patients have all been hospitalized at the Gallinger Municipal Hospital, a teaching institution of 1,650 beds in which because of limitations of the diet kitchen we have considered it best to limit our diet to three basic

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formulae, bringing the number of calories when necessary to a larger figure by the addition of butter or a meat sandwich with milk. The formulae of these three diets are as follows:

No. 1: C180, P60, F60 (3 meals with one third of the total glucose value per meal).

No. 2: C225, P70, F70 (3 meals with one third of the total glucose value per meal).

No. 3: C225, P70, F77 (3 meals with one fifth of the total glucose value at breakfast, two fifths at the noon meal, and two fifths at the evening meal).

After the patient is out of acidosis, if he entered the hospital in that state, or after he has become stabilized as well as possible in regard to any complication that may have existed or continues to exist, he is given the diet that he is to remain on for the duration of the investigation. This is No. 3 above, unless rare and special conditions lead to the use of one of the other diets. Later, in some cases, according to a considered need, a bedtime feeding of a meat sandwich and a glass of milk is added, usually when protamine zinc insulin is being used, or in a few cases a midafternoon feeding of similar content for patients receiving globin insulin.

In many cases when the patient's condition allows it on admission or soon afterwards his blood sugar curve is determined before insulin is given or after withdrawal of insulin for a day. This curve is made by determining the concentration of dextrose in samples of venous blood drawn at 7:00 a.m., 9:00 a.m., 11:00 a.m., 1:00 p.m., 4:00 p.m., 7:00 p.m., and 11:00 p.m. The analyses are made by a fulltime skilled technician or medical resident assigned to this work. The urine is collected for the 24 hours daily or as often as is needed to determine how much dextrose is being excreted on a given dose of insulin.

Insulin, either protamine zinc or globin, is then given each morning at 7:00 in an arbitrary amount and rapidly changed until the optimum amount is being used, rarely over 80 units, the state of the diabetes being ascertained by means of the amount of dextrose excreted in the urine in 24 hours and by blood sugar determinations made one hour after breakfast. When the amount of dextrose in the 24-hour urine becomes 5 grams or less and the blood sugar one hour after breakfast is 175 mg. per cent or less, if possible a blood sugar curve is made. The insulin is then rapidly changed to the other form and the procedure repeated. At least three days and usually a week has been allowed on each dose and form of insulin before making blood sugar curves. About half of the patients were treated first with each form of insulin and then changed to the other preparation.

#### MATERIAL

Of all the diabetic patients hospitalized during the period of this study 84 were treated for comparative purposes on both globin and protamine

zinc insulins with blood sugar curves obtained while they were being given an equal dose of each form of insulin. Some of these patients were similarly studied on other admissions with a total of 97 hospital admission case studies, providing 587 pairs of blood sugar values comparing globin insulin with protamine zinc insulin.

Careful scrutiny of each case has been used to be quite certain that changes in diet, exercise, infection, healing fractures, hepatic disease or other evident factors did not distort the comparison.

## RESULTS

A comparison of the blood sugar curves of these 97 case studies on both forms of insulin in equal doses gave the following results:

I. Number of patients controlled better by globin insulin than by protamine zinc insulin .....	70
1. Adequately (no blood sugars over 200) .....	50
2. Inadequately (at least one blood sugar over 200) .....	20
II. Number of patients better controlled by protamine zinc insulin than by globin insulin .....	22
1. Adequately (no blood sugar over 200) .....	19
2. Inadequately (at least one blood sugar over 200) .....	3
III. Number of patients well controlled by both forms, no blood sugar levels being over 175 mg. per cent .....	14
IV. Number of patients moderately well controlled by both forms, meaning that some blood sugar levels were between 175 mg. per cent and 200 mg. per cent .....	7
V. Number of patients not adequately controlled by either form of insulin, some blood sugar levels being 200 mg. per cent or more .....	24

These figures indicate definitely that for these 84 hospitalized patients with 97 comparisons of blood sugar values, using the same diet and the same number of units of each form of insulin, globin insulin was superior in bringing about control as judged by these rigid chemical criteria. On the other hand, there was a fair number of patients "inadequately controlled" by globin insulin on the regimen used at the time of the comparative curves; this does not mean, however, that these patients were incapable of being controlled adequately for ordinary clinical purposes on some other dosage or combination of insulins.

When these patients were compared with attention to all factors (blood sugar curve, hypoglycemia, and general state), 65 were controlled better with globin insulin, 25 with protamine zinc insulin, and seven equally well with the two forms in equal doses. This type of analysis is important in addition to that above, since a smoother blood sugar curve, avoidance of low blood sugar levels, and sense of well-being are desirable.

A comparison is made in table 1 of the blood sugar curves and 24-hour

TABLE I

Comparison of blood sugar curves and 24 hour urine sugar in patients receiving equal doses of globin zinc insulin and protamine zinc insulin, and no insulin

For each patient: a. Top Line—curve with globin zinc insulin (G)

b. Middle Line—curve with protamine zinc insulin (P)

c. Bottom Line—curve with no insulin (0)

Patient	Age	Units, Dose	Date	Blood Sugar Curve							Gm. Sugar 24 Hours Urine
				7:00 a.m.	9:00 a.m.	11:00 a.m.	1:00 p.m.	4:00 p.m.	7:00 p.m.	11:00 p.m.	
1	60	55-G 55-P 0	3/28/45 3/23/45	148 103	163 211	182 151	154 211	125 238	163 297	174 186	0 0
1	60	50-G 50-P 0	7/ 3/45 7/11/45	118 93	174 167	— —	186 108	87 129	85 129	89 125	0 27
2	53	20-G 20-P 0	4/20/45 4/10/45 3/ 9/45	53 81 250	143 121 222	157 114 258	89 140 297	78 138 258	83 190 364	95 167 320	0 0
3	43	80-G 80-P 0	6/10/45 6/ 7/45	174 267	— —	— —	276 444	— —	— —	— —	21 42
4	52	45-G 45-P 0	11/22/45 11/11/45	143 116	— —	138 182	154 138	— —	— —	— —	— —
5	34	25-G 25-P 0	11/20/44 11/13/44	— —	96 242	82 187	102 189	103 217	209 202	209 131	0 4.2
6	46	75-G 75-P 0	5/11/45 5/ 7/45 4/13/45	67 80 267	143 205 364	60 125 382	108 138 432	— — 364	— — 422	— — 304	0 0 11.3
7	46	40-G 40-P 0	5/ 1/45 4/24/45 4/ 9/45	161 77 211	250 95 333	167 69 100	228 95 333	200 174 216	250 235 216	276 138 222	9.9 6.3 30

TABLE I—Continued

Patient	Age	Units, Dose	Date	Blood Sugar Curve							Gm. Sugar 24 Hours' Urine
				7:00 a.m.	9:00 a.m.	11:00 a.m.	1:00 p.m.	4:00 p.m.	7:00 p.m.	11:00 p.m.	
8	52	15-G 15-P 0	5/28/45 6/1/45 5/17/45	174 118 235	129 216 308	129 133 182	242 167 235	77 81 143	182 182 222	108 105 174	0 0 0
9	80	30-G 30-P 0	9/28/45 11/8/45	95 83	105 129	83 118	118 161	133 143	— —	— —	0 0
10	50	40-G 40-P 0	7/2/45 6/26/45	87 62	143 121	160 129	200 108	160 91	105 154	180 91	— —
11	64	20-G 20-P 0	4/26/45 4/17/45 11/27/45	72 100 118	211 138 111	103 129 133	161 121 205	87 80 211	125 100 326	103 111 325	— — 5
12	63	10-G 10-P 0	3/13/45 3/5/45 2/17/45	133 182 195	200 235 286	235 242 186	— — 276	143 151 178	211 202 364	174 135 170	0 0 —
13	39	30-G 30-P 0	7/6/45 7/11/45 6/18/45	125 77 308	— — 320	114 154 250	138 154 320	182 133 267	— — 250	71 143 228	0 0 30
14	52	60-G 60-P 0	7/31/45 8/3/45	52 83	— —	74 121	154 200	91 170	143 205	56 161	0 0 —
15	57	25-G 25-P 0	7/24/45 7/19/45 12/21/44	103 97 125	160 167	149 129 286	174 216 297	138 95 250	143 143 220	103 129 160	0 0 0
16	73	15-G 15-P 0	7/11/45 7/3/45 5/23/45	91 91 190	138 134 211	62 111 267	167 122 320	154 83 286	71 78 320	67 89 216	— — 15

TABLE I—Continued

Patient	Age	Units, Dose	Date	Blood Sugar Curve								Gm. Sugar 24 Hours' Urine
				7:00 a.m.	9:00 a.m.	11:00 a.m.	1:00 p.m.	4:00 p.m.	7:00 p.m.	11:00 p.m.		
17	59	35-G 35-P 0	3/26/45 3/20/45 —	145 149 —	— — —	154 128 —	222 182 —	— — —	228 190 —	— — —	0 0 —	
18	60	45-G 45-P 0	4/26/45 5/17/45 3/24/45	67 134 444	200 151 445	100 160 —	73 160 333	64 105 362	85 157 340	77 154 280	0 0 1.3	
18	60	30-G 30-P 0	6/29/45 6/21/45 —	87 125 —	170 190 —	93 148 —	— — —	87 105 —	— — —	— — —	— — —	
19	44	25-G 25-P 0	10/ 4/44 11/ 2/44 —	145 125 —	235 242 —	160 242 —	235 153 —	129 161 —	190 218 —	267 135 —	— — —	
20	70	30-G 30-P 0	7/30/45 8/ 3/45 7/23/45	77 81 —	138 161 —	108 133 —	140 154 —	129 149 —	182 174 —	154 143 333	2.6 1.1 —	
21	25	80-G 80-P 0	7/ 5/45 7/13/45 —	71 191 —	167 286 —	111 333 —	174 500 —	108 364 —	211 333 —	154 222 —	1.6 19 —	
22	52	20-G 20-P 0	4/24/45 4/ 2/45 —	53 81 —	— — —	97 121 —	111 133 —	— — —	120 133 —	133 111 —	0 0 —	
23	65	20-G 20-P 0	10/27/45 10/15/45 9/26/45	100 133 157	118 143 211	95 154 450	— — 250	74 151 —	118 143 —	— — —	— — 17.5	
24	56	50-G 50-P 0	3/29/45 3/23/45 —	118 143 —	222 228 —	133 186 —	216 170 —	95 158 —	173 242 —	75 147 —	0 0 —	

TABLE I—Continued

Patient	Age	Units, Dose	Date	Blood Sugar Curve							Gm. Sugar 24 Hours' Urine
				7:00 a.m.	9:00 a.m.	11:00 a.m.	1:00 p.m.	4:00 p.m.	7:00 p.m.	11:00 p.m.	
25	68	60-G 60-P 0	8/17/45 8/23/45 8/ 4/45	— — 186	— — 286	133 118 —	170 148 —	143 138 —	— — 308	135 95 258	0 0 28
26	36	80-G 80-P 0	3/ 6/45 2/28/45 —	154 40 —	205 121 —	286 143 —	308 267 —	125 205 —	133 382 —	52 235 —	0 20 —
27	58	30-G 30-P 0	7/23/45 7/30/45 7/17/45	100 133 —	128 222 —	— — —	160 134 —	125 125 —	133 200 —	161 105 444	3.7 4.8 —
28	70	20-G 20-P 0	4/ 2/45 4/ 9/45 3/16/45	163 174 211	174 250 163	— — 222	— — 195	182 174 205	167 170 222	— — 175	0 0 0
28	70	30-G 30-P 0	4/26/45 4/16/45 —	83 71 —	105 108 —	70 143 —	114 121 —	91 111 —	103 133 —	95 108 —	— — —
29	70	25-G 25-P 0	5/ 1/45 5/16/45 4/ 6/45	174 70 333	85 95 —	87 103 —	70 211 —	60 258 286	151 267 308	75 163 —	0 2.0 —
30	53	75-G 75-P 0	11/28/44 11/21/44 —	70 43 —	67 108 —	105 86 —	128 348 —	— — —	110 198 —	94 89 —	0 33.9 —
31	43	30-G 30-P 0	3/26/45 3/19/45 9/20/44	75 74 187	149 151 235	154 205 —	167 200 —	108 85 —	163 182 —	138 151 —	0 0 —
32	60	30-G 30-P 0	4/24/45 5/ 2/45 4/ 7/45	138 77 182	149 190 195	— — 160	200 222 195	105 163 78	114 235 211	— — 149	0 9 —

TABLE I—Continued

Patient	Age	Units, Dose	Date	Blood Sugar Curve							Gm. Sugar 24 Hours' Urine
				7:00 a.m.	9:00 a.m.	11:00 a.m.	1:00 p.m.	4:00 p.m.	7:00 p.m.	11:00 p.m.	
33	56	65-G 65-P 0	5/ 2/45 5/25/45 —	— — —	182 108 —	114 170 —	258 138 —	150 62 —	182 170 —	211 182 —	0 0 —
33	56	55-G 55-P 0	4/23/45 4/18/45 —	138 143 —	— — —	— — —	— — —	200 200 —	286 276 —	— — —	5.9 6.7 —
34	42	50-G 50-P 0	8/13/45 8/21/45 —	87 89 —	— — —	77 118 —	— — —	97 211 —	133 191 —	— — —	12 10 —
35	52	40-G 40-P 0	11/16/44 10/31/44 10/17/44	59 57 267	275 83 —	225 229 —	270 317 —	218 303 —	247 412 —	223 84 —	11.7 22.8 54
36	60	20-G 20-P 0	3/14/45 3/ 5/45 2/19/45	85 125 286	— — —	120 122 —	100 143 —	— — —	91 70 —	83 68 —	0 0 22
37	53	25-G 25-P 0	10/31/44 11/13/44 9/13/44	136 93 235	195 85 195	190 86 —	160 133 —	77 93 —	186 94 —	207 51 —	0 0 21.4
38	56	30-G 30-P 0	3/ 7/45 2/23/45 —	154 100 —	186 211 —	— — —	190 222 —	104 163 —	218 235 —	178 200 —	0 0 —
38	56	40-G 40-P 0	5/28/45 5/ 8/45 —	138 133 —	190 195 —	67 148 —	121 195 —	63 178 —	114 145 —	148 149 —	— — —
39	52	20-G 20-P 0	5/18/45 5/ 8/45 4/19/45	105 114 250	— — —	103 125 —	178 167 —	— — —	— — —	— — —	0 1.2 —

TABLE I—Continued

Patient	Age	Units, Dose	Date	Blood Sugar Curve							Gm. Sugar 24 Hours' Urine
				7:00 a.m.	9:00 a.m.	11:00 a.m.	1:00 p.m.	4:00 p.m.	7:00 p.m.	11:00 p.m.	
40	59	30-G 30-P 0	1/ 9/45 2/ 1/45	143 97	— —	143 174	183 167	100 191	174 228	128 143	0 0
40	59	40-G 40-P 0	4/ 3/45 3/16/45	129 87	138 167	100 174	111 167	129 105	— —	114 74	— —
40	59	30-G 30-P 0	6/ 4/45 5/16/45	83 89	163 182	91 167	178 186	80 114	129 143	118 70	— —
40	59	25-G 25-P 0	7/ 3/45 6/24/45	108 95	160 195	148 205	235 129	124 182	— —	114 193	— —
41	48	10-G 10-P 0	7/ 7/45 7/13/45	129 87	— —	129 118	138 143	129 87	95 200	89 103	0 0
42	29	50-G 50-P 0	3/19/45 3/14/45 2/23/45	67 83 211	170 170 222	— — —	174 134 297	136 108 276	195 167 400	132 74 308	0 0 41
43	52	15-G 15-P 0	7/ 7/45 7/13/45 6/ 8/45	91 87	108 267	161 190 333	133 167 348	114 100	— —	133 200	0 2
44	36	25-G 25-P 0	12/18/44 11/28/44 11/16/44	148 125 173	222 190 229	105 151 179	186 168 245	125 138 186	— — 245	167 171 259	1.2 3.4 11.2
45	46	50-G 50-P 0	7/11/45 7/ 7/45 6/25/45	100 148	89 87	157 170	163 174	143 182 364	250 200	200 91	1.3 3.0



TABLE I—Continued

Patient	Age	Units, Dose	Date	Blood Sugar Curve							Gm. Sugar 24 Hours' Urine
				7:00 a.m.	9:00 a.m.	11:00 a.m.	1:00 p.m.	4:00 p.m.	7:00 p.m.	11:00 p.m.	
46	56	35-G 35-P 0	11/ 7/45 10/30/45	83 103	83 200	129 167	— —	250 200	— —	— —	— —
47	49	75-G 75-P 0	8/ 2/45 8/13/45 7/ 7/45	100 81	— 364	114 77	125 111	77 95	174 170	167 81	0 0
48	46	25-G 25-P 0	7/16/45 7/23/45 7/11/45	71 157 200	129 205	111 174	167 174 258	114 182 286	149 205 250	111 200 258	3.8 8.5 19.2
49	40	25-G 25-P 0	11/20/45 11/11/45 11/ 5/45	118 95 235	— —	149 105	133 178	186 128	182 190	— —	— —
50	73	50-G 50-P 0	4/ 9/45 4/17/45	100 121	182 216	144 170	149 157	54 174	— —	121 118	0 0
51	33	20-G 20-P 0	7/26/45 7/31/45 7/ 1/45	143 121 242	216 205	114 200 267	211 222 333	105 174 228	161 174 242	157 167 211	3.3 6.0 19.5
52	63	30-G 30-P 0	3/27/45 3/19/45 3/ 7/45	133 121 200	160 126 250	125 100 297	211 133 308	151 100 222	167 136 320	161 85 221	— — 3.2
52	63	35-G 35-P 0	4/23/45 4/12/45	125 129	138 151	69 108	93 182	53 114	118 149	174 118	— —
52	63	20-G 20-P 0	7/ 5/45 6/21/45	103 105	— —	182 62	125 157	120 114	105 100	— —	— —

TABLE I—Continued

Patient	Age	Units, Dose	Date	Blood Sugar Curve							Gm. Sugar 24 Hours' Urine
				7:00 a.m.	9:00 a.m.	11:00 a.m.	1:00 p.m.	4:00 p.m.	7:00 p.m.	11:00 p.m.	
53	50	30-G 30-P 0	10/ 2/45 10/ 8/45 9/27/45	133 190 333	138 267 308	— — 125	129 235 348	228 222 242	200 297 336	242 211 308	30 43 88
54	42	50-G 50-P 0	7/ 7/45 7/12/45 5/23/45	62 167 308	108 200 286	118 161 242	138 228 348	75 167 250	167 154 333	103 95 348	0 9.4 40
55	60	40-G 40-P 0	3/12/45 3/ 5/45 —	129 114 —	250 190 —	211 178 —	182 170 —	138 121 —	170 178 —	— — —	0 0 19
56	52	15-G 15-P 0	7/10/45 7/ 5/45 6/13/45	85 95 258	83 129 —	163 105 235	163 182 444	105 143 —	160 167 —	143 121 —	0 0 —
57	65	45-G 45-P 0	7/17/45 7/23/45 7/ 5/45	125 118 286	157 163 308	69 121 400	91 138 500	125 121 364	190 125 348	131 125 286	0 0 16
58	63	25-G 25-P 0	9/ 9/45 9/17/45 6/29/45	95 80 580	133 200 —	170 143 —	— — —	111 149 —	178 200 —	111 149 —	0 0 —
59	17	65-G 65-P 0	7/20/45 7/26/45 7/ 1/45	74 42 —	190 133 —	145 93 —	157 163 —	129 138 422	235 258 —	69 133 —	21.4 16.5 —
60	50	70-G 70-P 0	5/22/45 5/28/45 4/28/45	74 75 —	— — —	125 118 —	154 143 286	125 154 —	133 178 —	186 100 —	0 0 —
61	54	50-G 50-P 0	5/19/45 5/25/45 4/12/45	83 105 —	200 216 —	83 167 —	222 205 —	182 174 —	228 235 —	— — 382	0.3 2.6 —

TABLE I—Continued

Patient	Age	Units, Dose	Date	Blood Sugar Curve								Gm. Sugar 24 Hours' Urine
				7:00 a.m.	9:00 a.m.	11:00 a.m.	1:00 p.m.	4:00 p.m.	7:00 p.m.	11:00 p.m.		
61	54	70-G 70-P 0	7/30/45 7/23/45 —	118 178 —	95 308 —	129 182 —	143 182 —	95 148 —	105 222 —	124 114 —	20 3.2 —	
62	76	45-G 45-P 0	5/27/45 5/22/45 4/ 3/45	77 138 242	160 200 276	108 167 276	167 200 286	114 190 222	163 211 308	108 211 267	0 0.9 4.6	
63	68	25-G 25-P 0	10/16/44 9/19/44 —	111 62 —	174 90 —	111 110 —	105 150 —	87 148 —	125 172 —	— — —	— — —	
64	65	80-G 80-P 0	3/29/45 3/19/45 2/25/45	78 95 —	170 140 —	200 222 388	211 222 —	143 120 —	157 382 —	93 145 —	0 0 —	
65	41	65-G 65-P 0	4/30/45 4/10/45 —	60 151 —	— — —	103 222 —	108 267 —	60 242 —	100 320 —	66 276 —	— 13.1 —	
66	50	75-G 75-P 0	4/17/45 2/21/45 1/23/45	129 105 —	— — —	125 216 —	195 258 —	105 242 290	174 222 —	118 151 —	0 16.8 —	
67	65	35-G 35-P 0	2/15/45 2/10/45 1/19/45	103 70 276	— — —	— — —	154 95 —	103 105 —	149 250 258	103 134 —	0 0 —	
68	69	25-G 25-P 0	5/10/45 5/ 2/45 4/17/45	105 77 —	— — —	118 222 —	200 178 —	95 125 —	157 190 333	118 276 —	0 0 —	
69	75	45-G 45-P 0	7/11/45 7/19/45 6/22/45	167 80 477	167 250 400	118 118 400	121 222 500	69 174 297	148 267 400	111 200 348	0 0 40	

TABLE I—Continued

Patient	Age	Units, Dose	Date	Blood Sugar Curve							Gm. Sugar 24 Hours' Urine
				7:00 a.m.	9:00 a.m.	11:00 a.m.	1:00 p.m.	4:00 p.m.	7:00 p.m.	11:00 p.m.	
70	68	35-G 35-P 0	7/24/45 7/30/45 7/ 5/45	97 121 308	— — —	151 161 —	157 148 333	129 111 286	154 174 383	69 95 267	1.0 0 —
71	55	35-G 35-P 0	7/ 3/45 6/26/45 —	87 103 —	143 154 —	111 122 —	195 228 —	100 213 —	100 182 —	86 105 —	7.2 21 —
72	71	40-G 40-P 0	4/24/45 4/16/45 4/ 5/45	105 85 228	143 133 250	60 129 228	114 149 242	60 163 228	186 157 235	85 91 182	0 0 4.0
72	71	25-G 25-P 0	7/ 3/45 7/11/45 —	167 81 —	138 143 —	158 160 —	200 100 —	105 67 —	93 124 —	95 91 —	0 0 —
73	28	40-G 40-P 0	11/28/44 11/20/44 11/ 4/44	125 77 252	194 98 —	170 124 —	— — —	— — —	288 163 —	182 122 —	2.2 4.6 —
73	28	20-G 20-P 0	10/ 2/45 9/24/45 —	83 125 —	178 235 —	74 129 —	125 121 —	111 188 —	128 200 —	111 178 —	0 0 0
74	51	75-G 75-P 0	8/15/45 8/21/45 8/ 6/45	105 211 —	167 333 —	186 308 —	250 348 —	80 332 444	180 320 382	145 297 —	0 44 —
75	35	40-G 40-P 0	7/27/45 7/23/45 4/22/45	111 83 —	228 114 —	93 69 —	114 200 —	111 74 —	174 105 382	160 83 —	0 0 —
76	26	15-G 15-P 0	2/27/45 2/ 8/45 1/16/45	103 103 167	133 111 235	73 89 216	125 111 —	86 103 174	116 109 170	138 163 —	0 1.8 4.1

TABLE I—Continued

Patient	Age	Units, Dose	Date	Blood Sugar Curve							Gm. Sugar 24 Hours Urine
				7:00 a.m.	9:00 a.m.	11:00 a.m.	1:00 p.m.	4:00 p.m.	7:00 p.m.	11:00 p.m.	
77	37	40-G 40-P 0	7/ 3/45 7/ 7/45 6/18/45	125 83 320	143 200 400	114 97 —	125 149 422	77 67 242	129 133 422	111 124 242	4.0 0 32
78	64	20-G 20-P 0	7/24/45 7/30/45 7/ 7/45	134 125 —	— — —	186 97 —	235 205 —	143 148 325	182 200 —	160 134 —	0 0 14.2
79	54	45-G 45-P 0	9/17/45 9/22/45 9/12/45	161 222 —	89 190 —	133 222 —	— — —	— — —	— — 348	174 235 —	— — —
80	44	45-G 45-P 0	11/20/44 11/13/44 10/20/44	82 75 —	208 193 —	75 176 —	60 251 —	59 146 230	105 172 —	59 81 —	0 3.95 —
81	35	35-G 35-P 0	11/21/45 11/12/45 —	95 111 —	71 205 —	77 149 —	108 190 —	80 133 —	— — —	— — —	— — —
82	72	20-G 20-P 0	10/ 5/45 9/14/45 —	93 83 —	160 200 —	100 111 —	143 154 —	89 114 —	151 160 —	100 71 —	— — —
83	75	35-G 35-P 0	8/ 8/45 8/12/45 6/28/45	83 69 211	174 182 —	67 125 382	133 216 571	74 125 477	130 137 600	110 165 570	0 0 30
84	61	20-G 20-P 0	5/16/45 5/ 8/45 —	182 125 —	186 228 —	— — —	138 242 —	222 138 —	167 222 —	145 242 —	0 0 —

urinary output of sugar for the 84 patients studied in 97 hospital admissions while they were receiving: (a) globin insulin with zinc, (b) protamine zinc insulin in the same dosage, and (c) no insulin. From these data, composite blood sugar curves were made from the averages of blood sugars at each of the seven points of time and with each form of treatment for all the cases. These averages of the blood sugars, with the averages of the urinary sugar, are given in table 2.

TABLE II

Composite blood sugar curves and average 24-hour urinary dextrose excretion for 84 patients on 97 admissions on equal doses of globin insulin, protamine zinc insulin, and no insulin

Form of Insulin	Blood Sugar (mg. %)							Gm. Dextrose Sugar in 24 Hours' Urine
	7 a.m.	9 a.m.	11 a.m.	1 p.m.	4 p.m.	7 p.m.	11 p.m.	
Globin	109	159	125	161	116	157	131	1.9
Protamine Zinc	108	178	149	183	150	194	140	5.6
None	254	275	253	325	269	317	274	20.1

From these averages as shown in figure 1, it is evident that the blood sugar curve approached the normal trend more nearly with globin insulin than with protamine zinc insulin. Although the average fasting blood sugar was the same with the two forms, blood sugar levels were higher with protamine zinc insulin at all other times tested. Although the blood sugar

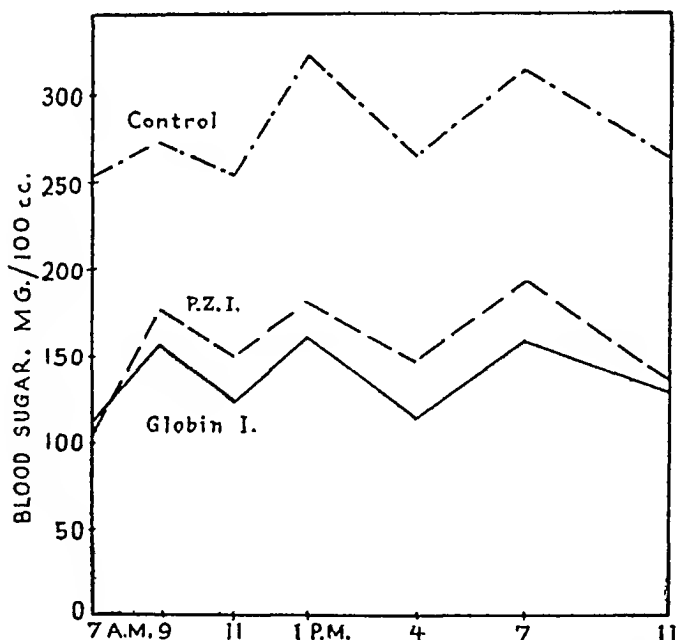


FIG. 1. Composite blood sugar curves based on 97 case comparisons obtained on 84 patients while receiving: (1) no insulin (Control), and equal doses of (2) globin insulin (Globin I.) and (3) protamine zinc insulin (P. Z. I.).

returned to normal before lunch, before supper and before midnight with globin insulin it was in the hyperglycemic range at these times with equal doses of protamine zinc insulin. The post-prandial rises were higher with protamine zinc insulin than with globin insulin.

These average blood sugar values were analyzed statistically by means of the "t" test in order to determine whether the differences between the values obtained with globin insulin and with protamine zinc insulin were significant. The "t" test and other statistical methods referred to in this paper are described in standard texts such as "Statistical Methods," 4th edition, 1946, by G. W. Snedecor, Iowa State College Press, Ames, Iowa. The values for "t" for the various time intervals from 7:00 a.m. to 11:00 p.m. were respectively, 0.188, 2.32, 3.39, 2.44, 4.17, 4.32 and 1.11. A value for "t" greater than 1.97 indicates that the probability is less than 1 in 20 that the two values being compared are merely chance variations, and the difference is considered significant; "t" greater than 2.6 indicates a probability of less than 1 in 100 that the two values are chance variations, and such a difference is regarded as highly significant.

It is seen that the average blood sugar values for globin insulin and protamine zinc insulin were not significantly different at 7:00 a.m. and 11:00 p.m. At each other time the average blood sugar level was significantly lower for globin insulin than for protamine zinc insulin; the "t" values indicate that these differences are not due to chance alone.

The data were also given a comprehensive treatment by an analysis of variance. The variation due to three major factors: (1) the difference between the two types of insulin; (2) the collection of blood samples at seven different time intervals; and (3) the difference between patients, was segregated and expressed as a variance. Each of these three variances was divided in turn by the variance due to experimental error and the three respective variance ratios or F values were found to be (1) 62.52, (2) 32.18, and (3) 4.16. These figures were then compared with their corresponding values in tables of distribution of F to determine whether they were significant. The large F value of 62.52 shows beyond question that globin insulin controlled the blood sugar better than protamine zinc insulin. As was to be expected, blood sugars were significantly different at various times of the day, and patients differed significantly from each other.

The averages of the 24-hour urinary sugar analyses were as follows: 1.9 grams with globin insulin and 5.6 grams with protamine zinc insulin. The average glycosuria of these patients was controlled better with globin insulin than with protamine. It is of significance that this occurred with the same preparation which gave more nearly normal control of the blood sugar curve.

The 24-hour urinary sugar data were also analyzed on the basis of frequency of incidence of glycosuria. Data were obtained on 76 patients with both globin insulin and protamine zinc insulin. Among these 76 patients, measurable glycosuria occurred in 33 cases with protamine zinc insulin and

20 cases with globin insulin. The chi-square was 4.9 with a value of  $P$  less than 0.05, that is, the probability is less than 1 in 20 that this difference would arise by chance alone; the incidence of glycosuria was, therefore, significantly less with globin insulin than with protamine zinc insulin under the conditions of these studies.

Likewise, of the 76 patients, there were 19 having glycosuria of more than 5 grams in 24 hours when protamine zinc insulin was used and only nine when globin insulin was used. The value for chi-square was 4.38, corresponding to a value for  $P$  of less than 0.05. The incidence of glycosuria of more than 5 gm. in 24 hours was, therefore, significantly lower with globin insulin than with protamine zinc insulin.

If the cases showing no glycosuria with either insulin preparation are eliminated, the differences are even more striking. Thus, a total of 35 cases had glycosuria with either globin insulin or protamine zinc insulin or both. Of these, 33 had glycosuria with protamine zinc insulin and 20 with globin insulin. In other words, there were only two cases having glycosuria with globin insulin that did not also have glycosuria with protamine zinc insulin. The value of chi-square for these data is 13, corresponding to  $P$  of less than 0.01, which indicates a highly significant difference in the results.

Similarly, of 20 cases in which there was glycosuria of 5 gm. per 24 hours or more, 19 had this degree of glycosuria with protamine zinc insulin and only nine with globin insulin. The chi-square value is 11.7,  $P$  is less than 0.01, and the difference is highly significant.

### ILLUSTRATIVE CASES

In the group of patients with comparable curves on equal doses of the two preparations, there were many in whom there was clear evidence that globin insulin was superior to protamine zinc insulin in controlling the blood sugar curve, while in a few cases the converse was found. In some patients, the curves on the two preparations were very similar. In other patients the curves showed great difference in the times at which the two preparations were most effective. Since the curves of all the cases cannot be produced here, only samples of the various trends will be shown.

1. S. P., Case 62, a 76 year old colored woman who had been a known diabetic for 15 years was admitted with back pain, polydipsia, polyuria, nocturia and hypertension. With no insulin, a blood sugar curve was high at all hours, with rises after each meal (figure 2). Protamine zinc insulin, 15 units, was started and raised to 45 units before the 24-hour urinary sugar fell below 5 gm. and the fasting blood sugar approached normal. A curve on the fourth day on this dose had all levels near 200 mg. per cent except the fasting and pre-lunch specimens. Globin insulin, 45 units, was then used instead of the protamine zinc insulin. On the fourth day after the change to globin insulin, a curve showed normal blood sugars before each meal and midnight, with rises to only 160 to 167 mg. per cent after each of the three meals. Thus, in this patient, better control occurred with globin insulin.

2. Y. I., Case 37, a 53 year old Japanese male, with known diabetes for five years, had mild hypertension and chronic nephritis. A curve after 19 days on 25 units of



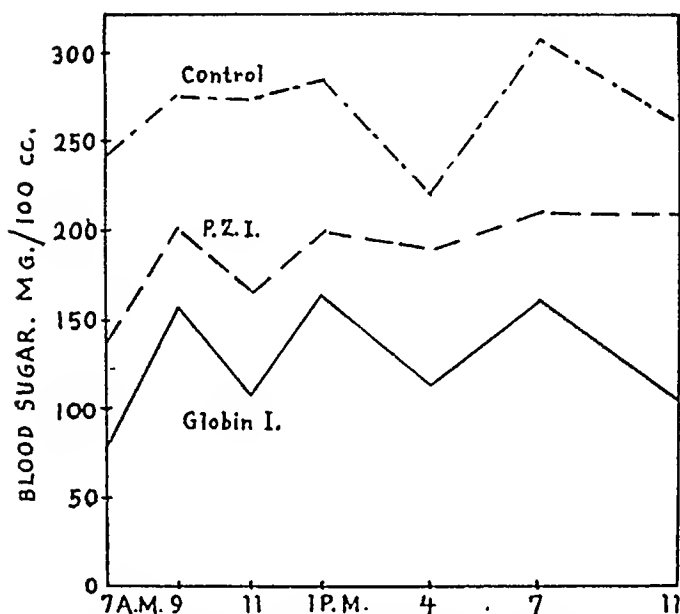


FIG. 2. Blood sugar curves of a patient (S. P., Case 62) receiving no insulin (Control), and, in turn, 45 units each of globin insulin (Globin I.) and protamine zinc insulin (P. Z. I.). Globin insulin gave better control.

globin insulin revealed blood sugars of 136 mg. per cent at 7:00 a.m. (fasting) and 77 at 4:00 p.m. At other hours tested the blood sugar was above normal, 160 to 207 mg. per cent (figure 3). After nine days on 25 units of protamine zinc insulin, the blood sugar was in the lower ranges of normal (85 to 95 mg. per cent) at each hour tested except for a rise to 133 mg. per cent after lunch and a fall to 51 mg. per cent at 11:00 p.m. Although this indicated better control of the blood sugar curve with protamine zinc insulin, a few days later the patient began to complain of mild clinical reactions to the protamine zinc insulin in the late afternoon even when the dose was dropped to 20 units. With doses of 15 to 20 units of globin insulin, he felt better, according to his statement and was discharged on this régime. Curves on these lower doses of globin insulin also indicated hyperglycemia after breakfast and supper, with reasonably good control of the blood sugar at other times.

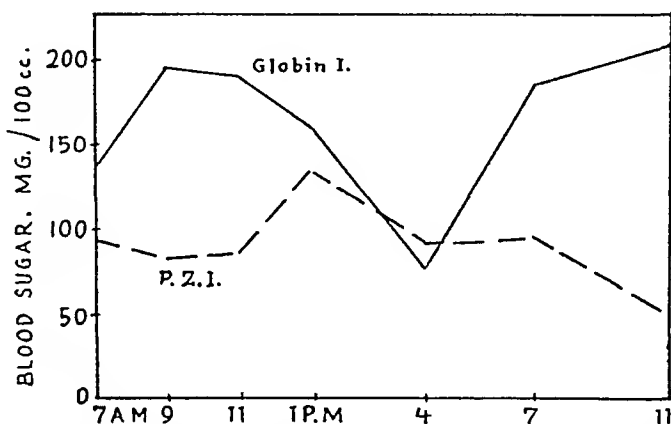


FIG. 3. Blood sugar curves of a patient (Y. I., Case 37), receiving, in turn, 25 units each of globin insulin and protamine zinc insulin. The latter provided a better curve, but induced mild clinical reactions not experienced with globin insulin.

3. J. M., Case 52, a 63 year old white male was admitted with gangrene of a toe and found to have diabetes mellitus with a blood sugar curve which was high at all hours when he was not receiving any insulin. After correction of the acute condition and rising doses of protamine zinc insulin a curve on the sixth day with 30 units daily showed a smooth curve which was normal throughout (figure 4). Eight days after being changed to 30 units daily of globin insulin a curve showed blood sugars of 125 to 211 mg. per cent. It would seem that in this instance the use of protamine

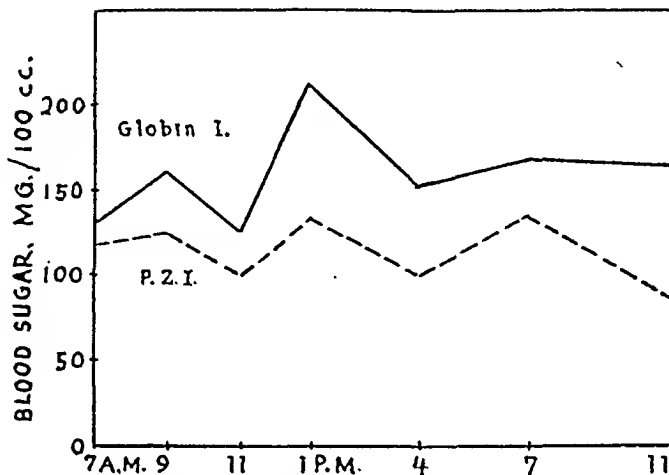


FIG. 4. Blood sugar curves of a patient (J. M., Case 52) showing better control with 30 units of protamine zinc insulin than with 30 units of globin insulin.

zinc insulin was preferable. On two subsequent occasions comparisons were made between the two preparations with dosages of 35 units and 20 units. From the data as shown in table 1 protamine zinc insulin might be considered preferable in this case.

4. A. H., Case 36, a 60 year old white woman, was found to be a mild diabetic after suffering an episode of hemiplegia. A blood sugar curve after seven days on 20 units of protamine zinc insulin closely resembled that made after nine days on 20 units of globin insulin (figure 5). However, the levels of 70 and 68 mg. per cent occurring after supper and at 11:00 p.m. with protamine zinc insulin were lower than one likes to see in an elderly diabetic patient. Within the next two months, this patient's requirement for insulin gradually fell to zero. This case is representative

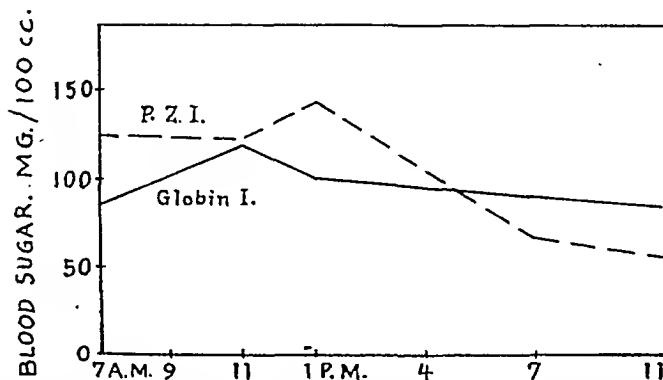


FIG. 5. Blood sugar curves of a patient (A. H., Case 36) receiving, in turn, 20 units each of globin insulin and protamine zinc insulin. Good control was obtained with either preparation.

of a group in which either form of insulin seems just about as effective as the other; this group is generally composed of rather mild diabetic patients, needing less than 25 units of insulin daily with a measured diet.

5. A. G., Case 26, a 36 year old severe diabetic patient, is illustrative of a group in which two forms of insulin showed striking differences in the degree of effectiveness at different hours. A known diabetic for three years, she developed acidosis and coma after omitting her usual daily dose of 30 units of protamine zinc insulin. Following correction of this her daily need for insulin was found to have increased greatly. One month after admission and the fifth day on 80 units of protamine insulin, her blood sugar curve showed a fasting level of 40 mg. per cent, rising rapidly throughout the entire day to a peak of 382 mg. per cent at 7:00 p.m. and falling only to 235 mg. per cent by 11:00 p.m. (figure 6). On the sixth day after the

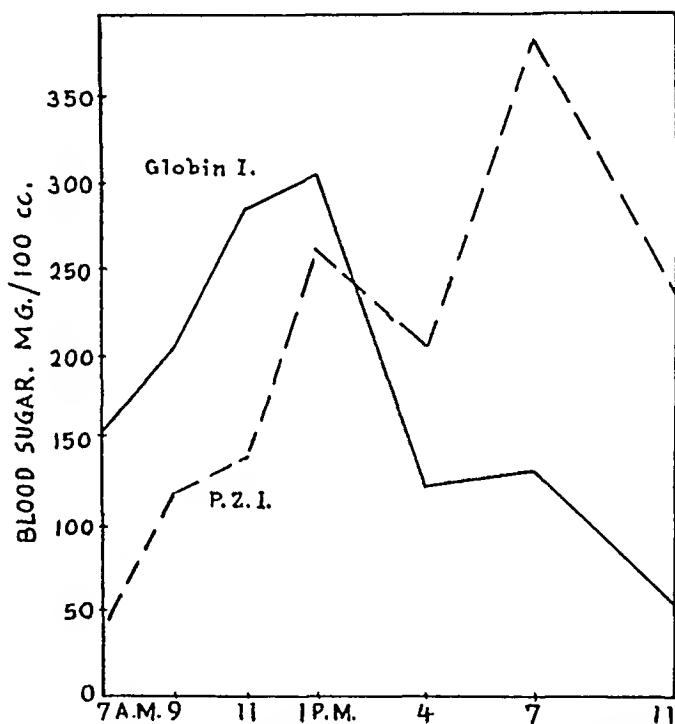


FIG. 6. Blood sugar curves of a patient (A. G., Case 26) receiving, in turn, 80 units each of globin insulin and protamine zinc insulin. Neither preparation gave good control. Note the different timing of effectiveness of the two preparations.

protamine zinc insulin was changed to 80 units of globin insulin, the curve showed wide variations from a low level of 52 mg. per cent at 11:00 p.m. to 308 mg. per cent at 1:00 p.m. The only really normal levels occurred with protamine zinc insulin after breakfast and before lunch, and with globin insulin before supper and after supper.

As examples of the fact that globin insulin may give better control of the diabetic state than protamine zinc insulin when large doses of insulin are required, figures 7, 8 and 9 show curves of three patients receiving 80, 75 and 70 units of insulin respectively. This result is contrary to statements made by some authors, who thought that globin insulin might be unsatisfactory for patients with severe diabetes needing more than 40 units of insulin daily.

Not considering the comparison of the two forms of insulin in equal doses

we have studied in the hospital 192 patients treated with globin insulin, although not all of these were available for a sufficient period to allow determination of the possibility of adequate control. Of the whole group, 88 (45.8 per cent) were well controlled, with no blood sugars above 175 mg. per cent; 39 (20.3 per cent) were moderately well controlled, with some blood sugars between 175 and 200 mg. per cent; and 65 (34 per cent) were inadequately controlled, with at least one blood sugar above 200 per cent. Thus, there were 127 (66.1 per cent) well controlled or moderately well con-

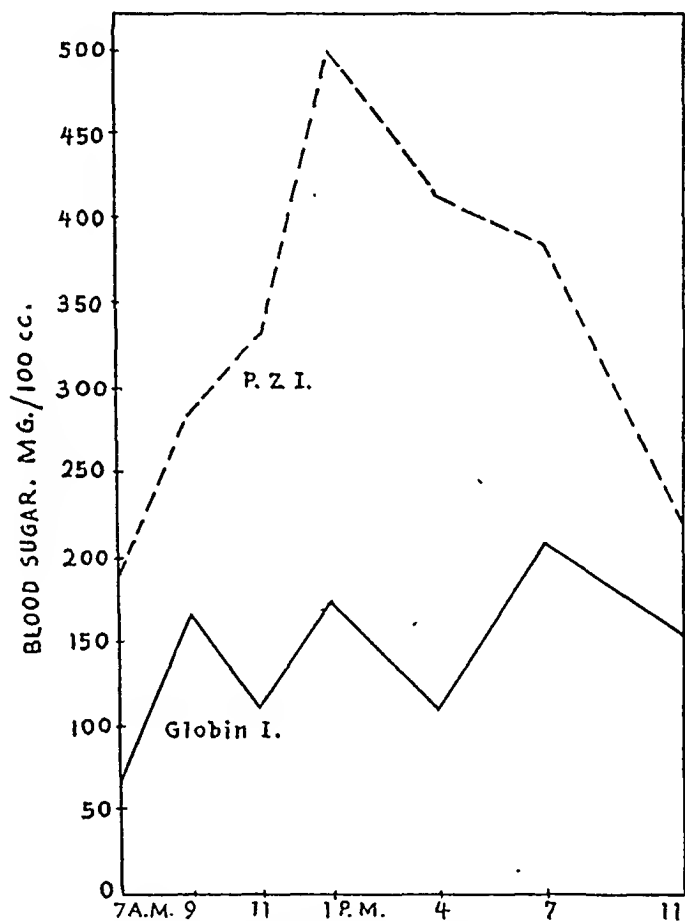


FIG. 7. Blood sugar curves for a patient (G. D., Case 21) showing much better control with 80 units of globin insulin than with 80 units of protamine zinc insulin.

trolled by globin insulin in the dosages used. Of the other 65 patients, an unknown number might have been so controlled had a better opportunity been afforded or if the rather arbitrary and elaborate criteria for control had not been adhered to so strictly. Generally these were patients who refused advice or care.

The statement has been made that globin insulin does not continue to be effective throughout the night to a degree capable of controlling the blood sugar during the night and before breakfast or to control the blood sugar

during the morning after breakfast. In our experience this difficulty has not been very common. Generally in the patients with comparable curves we have found that the fasting blood sugar, late night blood sugar, and the blood sugars during the morning after breakfast have been controlled fully

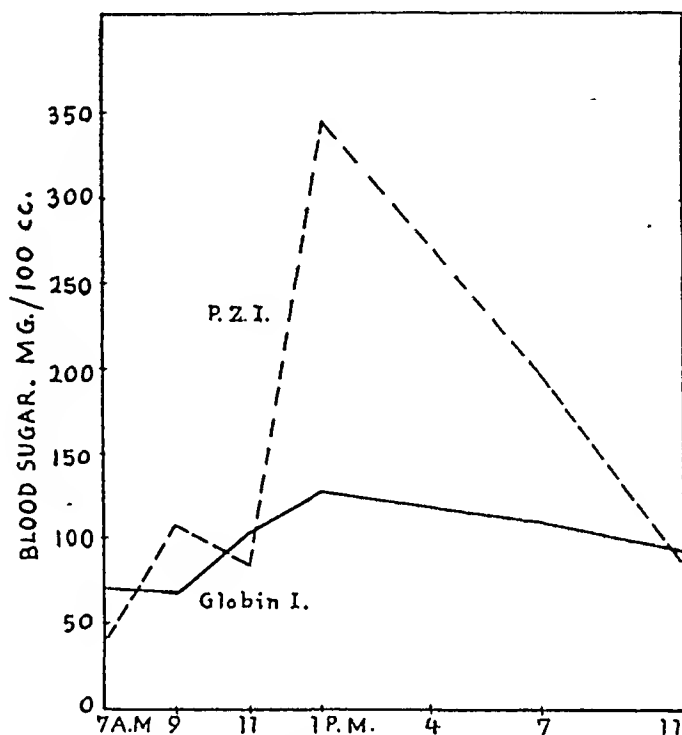


FIG. 8. Blood sugar curves of a patient (S. H., Case 30) showing good control with 75 units of globin insulin but poor control with 75 units of protamine zinc insulin.

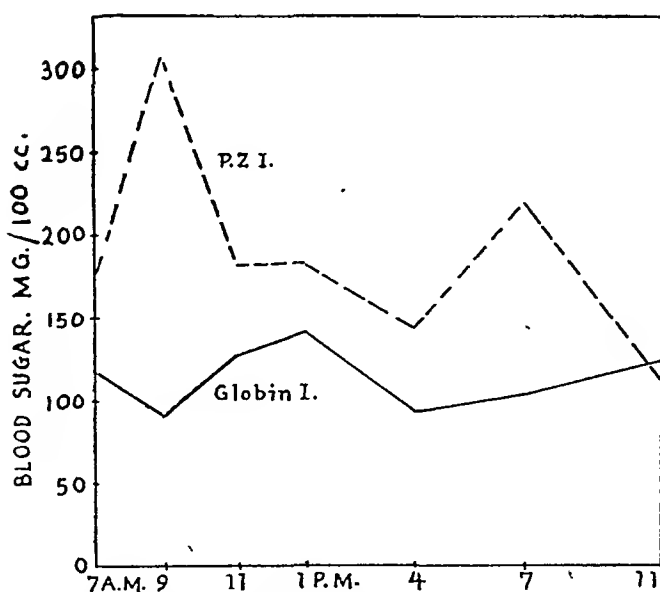


FIG. 9. Blood sugar curves of a patient (M. P., Case 61) showing excellent control with 70 units of globin insulin, but poor control with 70 units of protamine zinc insulin.

as well or better with globin insulin than with protamine zinc insulin. As indicated by the averages in table 2 and figure 1 the fasting and 11:00 p.m. blood sugar levels were practically identical with the two preparations, and the averages for the 9:00 a.m. blood sugar level taken an hour after breakfast and for the 11:00 a.m. blood sugar level taken just before lunch were more nearly normal with globin insulin.

### INSULIN REACTIONS

A record was kept of three types of reactions to insulin: (a) systemic, (b) purely chemical, and (c) local. In the group of 84 hospitalized patients with blood sugar curves compared on 97 occasions while getting the same dosage of the two preparations, there was only one mild systemic reaction while the patients were getting globin insulin, and five systemic reactions while they were getting protamine zinc insulin (three mild, two moderate).

Taking blood sugars of 70 mg. per cent and under as indicating hypoglycemia from a purely chemical viewpoint, there were 24 instances of this kind while the patients were getting globin insulin and 26 while they were receiving protamine zinc insulin in equal doses. There were no severe local reactions while the patients in this group were receiving globin insulin and only one while they were getting protamine zinc insulin in equal doses. Minor local reactions were elicited by careful quizzing in one of these patients while he was getting protamine zinc insulin and in only two while they were getting globin insulin. This group of patients was receiving globin insulin mixed with glycerin. Formerly, while globin insulin not mixed with glycerin was being used there were a few local reactions, but these were eliminated when the glycerin preparation was substituted.

Because of systemic or chemical hypoglycemic reactions a small feeding was given from 2:30 to 3:00 p.m., in some of the more severe and fluctuating cases while globin insulin was being given, since the reactions occurred shortly after this time. In this way the reactions were obviated. This was not needed by any of the patients whose blood sugar curves were compared on equal doses of the two preparations. Likewise, a small feeding is often necessary at about 9:00 p.m. for some patients while they are receiving protamine zinc insulin and occasionally when they are getting globin insulin in order to avoid nocturnal reactions. In the present group, however, this was needed by only two patients with protamine zinc insulin and one with globin insulin. These feedings were usually a meat sandwich and a glass of milk.

In the larger group of all patients given globin insulin and observed by us, severe hypoglycemic reactions have occurred only to patients who received very large overdosage, while omitting food; these patients were neglected grossly before arrival at this hospital, and similar reactions would be expected with any insulin under such conditions.

## DISCUSSION

It appears to us from the experience gained by this comparison of the two slowly acting forms of insulin that both are satisfactory preparations in the treatment of a large percentage of diabetics. Although each form is better than the other in some patients, more of them were controlled more satisfactorily with globin insulin. The comparison we have made with equal doses of the two preparations does not show necessarily the true effectiveness of either for all cases, however, since a larger dose of one or the other, or a complementary dose of regular insulin, usually before breakfast, might have been expected to bring about a little more satisfactory control in some instances. Most of these patients were controlled as well as possible, however, by one preparation or the other under the circumstances at the time. In the literature Bauman,<sup>1-5</sup> Marks,<sup>6</sup> Duncan and Barnes,<sup>7</sup> Bailey and Marble,<sup>8</sup> Paul,<sup>9</sup> Greenhouse,<sup>10, 11</sup> Mosenthal,<sup>12</sup> Protas,<sup>13</sup> Eaton,<sup>14</sup> Martin, Simonsen and Homann,<sup>15</sup> Margolin,<sup>16</sup> Ricketts,<sup>17</sup> Trasoff, Borden and Mintz,<sup>18</sup> Jackson and McIntosh,<sup>19</sup> Irwig,<sup>20</sup> Reiner, Lang, Irvine, Peacock and Evans,<sup>21</sup> Andrews and Groat,<sup>24</sup> Levitt and Schaus,<sup>25</sup> Colwell<sup>26</sup> and others have reported that the use of globin insulin was satisfactory to them or their data indicated that this might be so. Page and Bauman<sup>4</sup> found that cutaneous reactions to globin were less frequent than to protamine in both allergic and nonallergic patients. Lawrence,<sup>22</sup> Murphy,<sup>23</sup> Peck and Schechter,<sup>24</sup> Marble,<sup>25</sup> MacBryde and Reiss,<sup>26</sup> Jordan,<sup>27</sup> MacBryde,<sup>28</sup> DelFierro and Sevringhaus,<sup>29</sup> Malins,<sup>30</sup> concluded that there was no advantage or that there even was objection to the use of globin insulin except for patients who were sensitive to protamine zinc insulin. Some authors, for example, MacBryde and H. K. Roberts,<sup>31</sup> think that confusion results from the introduction of this additional preparation and that only unmodified or crystalline insulin and protamine zinc insulin are needed.

There is a trend on the part of some authors (Colwell and Izzo,<sup>32</sup> Adlersberg and Dolger,<sup>33</sup> and some others cited above) to use mixtures of crystalline insulin and protamine zinc insulin, most popularly 2 to 1 and 3 to 1. A mixture of these two preparations in the bottle or in the syringe, with the ratio varying according to daily needs, may be effective in the hands of very conscientious and intelligent patients, but is unsatisfactory for many patients. We believe that some authors are over-emphasizing the necessity of such a method in a large number of cases. We still think that the use of a single, long-acting insulin is preferable whenever satisfactory control can be attained and that this is possible in a very large percentage of cases with either globin insulin or protamine zinc insulin. Since the preparation of choice for any patient is the one which works best for that individual, globin insulin, protamine zinc insulin, or each should be tried before using mixtures of insulins or unusual timing of insulin administration.

Our experience with handling the mixtures of protamine and regular insulins has shown that these may be very confusing to many physicians or patients even in a teaching hospital.

In each of our very difficult cases in which very large doses of insulin were necessary or in which the diabetic state was very labile, best results have been obtained often by giving two doses of globin insulin (about 70 per cent of the needed amount before breakfast, the rest at 3:00 p.m.). This has been much simpler for both the patients and physicians than treatment with various mixtures of two or three forms of insulins.

The infrequent hypoglycemic reactions to globin insulin may be controlled usually by a small midafternoon feeding. Local reactions to globin insulin with glycerin have been insignificant in this group of patients.

### CONCLUSIONS

Globin insulin (prepared with zinc and glycerin) is a safe and useful preparation for the treatment of diabetic patients. Globin insulin controls the blood sugar curve and glycosuria in a more nearly normal way in more cases than an equal dose of protamine zinc insulin. Globin insulin as now prepared with glycerin is free of significant local reactions or allergy. The tendency to midafternoon hypoglycemia with globin insulin is preferable to nocturnal reactions which are likely to be severe with protamine zinc insulin. The majority of patients with diabetes who require insulin can be adequately controlled by a single dose of either globin insulin or protamine zinc insulin.

*Note:* We are indebted to the following Residents on the Diabetic Service for their persistence and enthusiastic cooperation in making possible this investigation: Drs. S. W. Kirstein, W. M. Goodman, M. H. Lepper, A. B. Coleman, F. Wilhelm, Wm. Kurstin, S. D. Loube, R. W. Merkle, W. F. Oliver, S. Kling, W. S. Schweikert, and B. A. Fitzgerald, and to the many others who helped in any way.

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# FURTHER OBSERVATIONS ON BLOOD GROUPING IN POLIOMYELITIS \*

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## INTRODUCTION

THE selective distribution of paralytic cases of poliomyelitis is well recognized but no explanation of the phenomenon has been offered which has found general acceptance. Epidemiological data are interpreted by some to suggest that the haphazard spread of paralysis is caused by limiting factors germane to the mode of virus dissemination. Other observers, mostly on clinical grounds, believe that the paralytic case represents only the rare accident in a long chain of abortive infections, occurring in especially predisposed individuals. Although the available knowledge does not permit a clear decision, the weight of evidence would seem to rest with the second hypothesis.

The predisposing factors that may contribute to the severe involvement of the central nervous system are probably exogenous as well as endogenous. Some of the former, such as fatigue, tonsillectomy and insolation, were studied experimentally and found to be instrumental in opening up peripheral portals of entry or breaking down neural defense mechanisms. The problem of endogenous predisposition, on the other hand, depending as it does upon the constitutional make-up and hereditary stigmatization of the individual, is too complex to lend itself to profitable experimentation at this time. Certainly, earlier attempts to secure an experimental basis for the significance of endocrine dysfunction or vitamin deficiency have failed to provide an unequivocal answer. A purely empirical approach, however, is possible by examining the distribution of blood group genes among poliomyelitis patients as compared with suitable control populations.

## EXPERIMENTAL

Since 1930, when blood grouping in poliomyelitis was begun, a considerable amount of information has accumulated over a period of years. Yet proper evaluation of the data is hampered for several reasons. In the first place, much of the published material is concerned with small series which lack statistical significance. Moreover, in some instances paralytic and non-paralytic cases, without distinction, were tabulated together; in others, the series included admittedly a majority of non-paralytic patients.

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The necessity for separating the two types of cases is self-evident from the nature of the problem. Selection of the control material, finally, has not always met the requirements as to geographical and chronological homogeneity as postulated by Schiff.<sup>1</sup> In table 1 we have brought together the figures of 10 series published by various investigators<sup>2-12</sup> from different parts of the world.

TABLE I  
Blood Grouping in Poliomyelitis

Series	Author	Locality	Year	Cases	Number	O	A	B	AB
I	Grooten and Kossovitch	France	1930	Poliomyelitis (all cases)	78	(%) 29.1	(%) 56.4	(%) 14.5	(%) 0
	Grooten and Kossovitch	France	1930	Normal	100	37.7	39.6	16.9	5.8
II	Jungeblut and Smith Ottenberg	N. Y. City	1916	Poliomyelitis (paralytic)	208	51.9	32.2	6.7	8.2
		N. Y. City	1921	Normal	286	44.0	42.0	12.0	2.0
III	Jungeblut and Smith Jungeblut and Smith Jungeblut and Smith Jungeblut and Smith Tiber	N. Y. City	1931	Poliomyelitis (all cases)	343	42.5	39.9	12.5	5.1
		N. Y. City	1931	Poliomyelitis (paralytic)	236	46.6	38.1	10.6	4.7
		N. Y. City	1931	Poliomyelitis (abortive)	107	33.6	43.9	16.8	5.6
		N. Y. City	1931	Normal	1000	45.6	35.7	14.0	4.7
		N. Y. City	1925/29	Normal	10,000	45.6	36.4	13.5	4.5
IV	Shaw et al.	San Francisco	1931	Poliomyelitis (all cases)	100	57.0	37.0	6.0	0
	Shaw et al.	San Francisco	1931	Normal	100	43.0	43.0	11.0	3.0
V	Blotevogel and Blotevogel	Germany	1928/33	Poliomyelitis (paralytic)	366	53.0	34.7	6.8	5.5
	Blotevogel and Blotevogel	Germany	1928/33	Normal	3500	41.4	43.4	10.1	5.1
VI	Hatzky	Germany	1933	Poliomyelitis (all cases)	131	38.2	43.5	16.8	1.5
	Hatzky	Germany	1933	Normal	9111	43.4	46.6	6.8	3.2
VII	Madsen et al.	Denmark	1934	Poliomyelitis (all cases)*	1118	43.4	41.7	10.0	4.9
		Denmark	1934	Normal	19,417	42.6	42.4	11.4	3.6
VIII	Erb et al. Erb et al. Erb et al. Erb et al.	Canada	1938	Poliomyelitis (all cases)	703	48.4	37.7	11.5	2.4
		Canada	1938	Poliomyelitis (paralytic)	427	50.8	37.5	9.8	1.9
		Canada	1938	Poliomyelitis (abortive)	276	44.6	38.0	14.1	3.3
		Canada	1938	Normal	1000	44.7†	40.8	11.6	2.9
		Canada	1938	Normal	1000	44.7†	40.8	11.6	2.9
IX	Kleinschmidt Kleinschmidt Kleinschmidt Kleinschmidt	Germany	1939	Poliomyelitis (all cases)	309	41.8	45.0	9.4	2.6
		Germany	1939	Poliomyelitis (paralytic)	211	46.0	43.6	8.1	2.4
		Germany	1939	Poliomyelitis (abortive)	98	32.7	51.0	12.2	4.1
		Germany	1939	Normal	1100	42.0	44.5	11.0	2.5
		Germany	1939	Normal	1100	42.0	44.5	11.0	2.5
X	Fanconi Fanconi	Switzerland	1944	Poliomyelitis (all cases)	507	37.3	53.5	7.0	5.0
		Switzerland	1944	Normal	1000	40.2	48.0	9.2	2.6

\* This series included only 47 paralytic cases.

† Corrected figure (personal communication).

An inspection of table 1 will show that in five series (II, III, V, VIII, IX) in which paralytic patients are listed, group B occurs with lesser frequency among the poliomyelitis patients than among the corresponding normal control individuals. The difference is not very great but recurs consistently in each of the five series mentioned. On the other hand, in the known abortive cases (series III, VIII, IX) group B occurs with a slightly higher frequency although only a few such comparisons are available. The comparison of unclassified cases, including an unknown percentage of paralyzed and abortive cases, may therefore be misleading. However, when

unclassified cases (series I, IV, VI, VII, X) are considered, with this reservation in mind, the diminished incidence of group B among the poliomyelitis patients appears again in four series (I, IV, VII, X) but is generally of smaller magnitude; one series (VI) shows an increase of group B for the poliomyelitis patients as compared with the normal controls. The deficit arising from this B shortage is mostly compensated for by an increased incidence of group O (II, IV, V, VII, VIII, IX), especially when paralyzed cases are considered; in one series (III) the increment is spread between groups O and A, while in the two remaining series (I, X) it is chiefly confined to group A. Variations in blood group AB are not being considered here because the figures are too small to warrant separate discussion.

Further interest was added when Kleinschmidt<sup>2</sup> first segregated the subgroups  $A_1$  and  $A_2$ , which comprise blood group A, in poliomyelitis patients. The figures recorded for paralytic cases showed a  $A_1/A_2$  ratio of 1:2.5, as compared with the normal ratio of about 1:4 (Mueller and Dahr<sup>13</sup>). Expressed by the relation  $\frac{A_2 + A_2B}{A_1 + A_1B}$ , 211 paralytic cases showed an index of 0.45 against an index of 0.29 for 98 non-paralytic cases. The index for 416 normal Germans is given as 0.19 by Dahr, Offe and Weber.<sup>14</sup> In other words, there was a notable increase of  $A_2$  at the expense of  $A_1$  in the poliomyelitis patients with paralysis. The same author determined for the first time the distribution of the blood antigens M and N in poliomyelitis patients and found the type N somewhat increased over the normal frequency (N in paralyzed poliomyelitis cases = 29.33 per cent; N in normal individuals = 21.5 per cent). Kleinschmidt's final conclusions were that individuals having blood groups O,  $A_2$  or factor N are predisposed to infection with paralytic poliomyelitis, whereas individuals with blood groups  $A_1$ , B or factor M tend to acquire the non-paralytic form of the disease.

The data to be reported in this paper are based on blood group determinations of 220 poliomyelitis patients. Groups O,  $A_1$ ,  $A_2$ , B,  $A_1B$  and  $A_2B$  were determined for the entire series; 187 patients were furthermore typed for the Rh<sub>0</sub> factor. In addition, 116 samples of saliva from selected poliomyelitis patients with the blood groups  $A_1$ ,  $A_2$ , B,  $A_1B$  and  $A_2B$  were examined for the absence or presence of the corresponding blood group substance. In accordance with established practice, persons having this substance in their saliva are designated "Secretors" as contrasted with "Non-secretors" who lack it. As is well known, the ability or inability to secrete group-specific substance in saliva represents a constant trait of the individual and is hereditary in character.

The series of 220 poliomyelitis patients consisted of 219 white individuals and one colored person. All but 29 cases had occurred during the 1944 epidemic of the Greater New York area; the remaining 29 persons were 1945 cases. The majority of the patients were children under 10 years of age. All were authentic cases of poliomyelitis with variable paralytic involvement, 190 cases being classified as moderate to severe and 30 as light.

None was of the abortive or non-paralytic type. The patients were hospitalized at the following institutions: New York State Reconstruction Home (172 cases); Grasslands Hospital (10 cases); Hospital for Joint Diseases (13 cases); Hospital for Special Surgery (25 cases). We are indebted to Drs. K. Landauer, G. Dalldorf, J. Blair, and P. D. Wilson for their co-operation and permission to study these cases. Our thanks are also due to Mr. R. Amado of the N. Y. State Reconstruction Home for valuable assistance in supplying necessary clinical information. The control material for the distribution of the four blood groups in normal individuals was obtained from the Blood Bank of Presbyterian Hospital, New York City. We are offering the records of a total of 20,211 normal donors, mostly residing in the Greater New York area, who were typed between November 1942 and May 1945. For further comparison of the frequencies of subgroups  $A_1$  and  $A_2$  among normal people there is listed a series of 1077 white individuals (N. Y. 1933-1943) published by Wiener.<sup>15</sup> Control material for determination of the frequency of "Secretors" and "Non-secretors" among normal individuals was obtained by typing the saliva of 111 selected normal medical students of the College of Physicians and Surgeons, Columbia University, with blood groups A, B, or AB. Additional control figures are provided by two published series of Schiff<sup>16</sup> and Wiener,<sup>15</sup> respectively.

The tests were carried out by typing freshly collected unknown red cells against known group A II (anti-B) and group B III (anti-A) human sera by the open well slide technic. The sera were obtained from Dr. Wiener's Laboratory, including the absorbed B serum for the segregation of subgroups  $A_1$  and  $A_2$ . Determination of the  $Rh_0$  factor was carried out with Wiener's anti- $Rh_0$  serum using the test tube technic recommended by this author. Tests to determine the presence or absence of blood group substance in saliva (Secretors and Non-secretors) were run in the following manner: Freshly collected saliva was inactivated by placing in boiling water for 10 minutes in order to destroy any enzymes present. One drop of heated saliva, in a dilution of 1:10, was mixed with one drop of properly diluted A or B serum containing 6 units of agglutinin. After standing for 15 minutes, 1 drop of a standard 2 per cent red cell suspension, A or B, was added to the saliva-serum mixtures. Controls with saline instead of saliva accompanied each test. The reactions were read macroscopically and microscopically after an interval of one hour at room temperature. Inhibition of specific agglutination was taken to indicate the presence of blood group substance in the sample of saliva, whereas the saliva was considered to be free from such substance when agglutination occurred specifically.

The results obtained in these various tests on poliomyelitis patients, together with the corresponding control material, are presented in tables 2, 3 and 4.

It will be seen from table 2 that the blood group distribution among the poliomyelitis patients differed in several respects from the normal control figures. Thus, there was a slightly lower incidence of blood group B (10.9

TABLE II  
Blood Grouping in Poliomyelitis

Series	Author	Locality	Year	Cases	Number %	O %	A %	A <sub>1</sub> %	A <sub>2</sub> %	B %	AB %	A <sub>1</sub> B %	A <sub>2</sub> B %	Index A <sub>2</sub> +A <sub>2</sub> B A <sub>1</sub> +A <sub>1</sub> B
XI	Jungeblut, Karowe and Braham Jungeblut, Karowe and Braham Wiener	Greater New York	1944/45	Poliomyelitis (paralytic)	220	42.72 (94)	43.18 (95)	27.27 (60)	15.90 (35)	10.90 (24)	3.18 (7)	2.27 (5)	0.90 (2)	0.56
		Greater New York	1942-1945	Normal	20,211	45.49 (9195)	36.41 (7359)			13.60 (2749)	4.49 (908)			
		Greater New York	1933-1943	Normal	1077	41.7	37.9	29.0	8.9	13.9	6.6	5.2	1.4	0.30

The figures given in parenthesis represent absolute numbers.

TABLE III  
Distribution of Rh<sub>0</sub> Factor in Poliomyelitis Patients

Cases	Number	Rh <sub>0</sub> positive	Rh <sub>0</sub> negative
Poliomyelitis (paralytic)	187	81.3% (152)	18.7% (35)
Normal	~	85%	15%

TABLE IV  
Secretion of Blood Group Substance in the Saliva of Poliomyelitis Patients

Author	Cases	Locality	Number	Secretors	Non-secretors
Jungeblut, Karowe, Braham	Poliomyelitis (paralytic)	New York			
	A		87	73.56% (64)	26.43% (23)
	A <sub>1</sub>		56	75% (42)	25% (14)
	A <sub>2</sub>		31	71% (22)	29% (29)
	B		23	65.21% (15)	34.78% (8)
	AB		6	50% (3)	50% (3)
	A <sub>1</sub> B		5	60% (3)	40% (2)
	A <sub>2</sub> B		1	0% (0)	100% (1)
	A, B, AB		116	70.69% (82)	29.3% (34)
Jungeblut, Karowe, Braham	Normal (A, B, AB)	New York	111	81.98% (91)	18.02% (20)
Schiff	Normal	New York	74	82.4%	17.6%
Wiener	Normal	New York	130	82%	18%

per cent) among the paralytic patients as compared with the normal expectancy (13.6-13.9 per cent). In contrast to earlier observations, the figures for blood group O were somewhat lower while those for blood group A were slightly higher in the poliomyelitis patients than in the normal controls. Further examination, however, shows that the increase in blood group A (43.2 per cent against 36.4-37.9 per cent) was brought about essentially by a higher frequency of subgroup A<sub>2</sub>. This is seen not only from the increase in the absolute frequency of A<sub>2</sub> (15.9 per cent against 8.9 per cent)

but also from the change in the relationship between  $A_1$  and  $A_2$  as expressed by the index  $\frac{A_2 + A_2B}{A_1 + A_1B}$  (0.56 against 0.30). As far as the incidence of the Rh<sub>0</sub> factor is concerned, the data given in table 3 do not indicate any significant deviation from the normal figures. The frequency of "Secretors" and "Non-secretors," on the other hand, as shown in table 4, reveals again abnormal figures for the poliomyelitis patients in that the percentage of "Non-secretors" was appreciably elevated (29.3 per cent for poliomyelitis patients against 18 per cent for normal individuals).

To illustrate once more the difference in the blood group pattern of paralytic patients as contrasted with that found in normal individuals, we have brought together in table 5 the records of the two poliomyelitis series in New York of 1931 and 1944/45 with the corresponding normal local figures, supplemented by older and more recent records from normal populations in a number of larger cities from various parts of the United States.<sup>17</sup> Repetition of the characteristic features (slight elevation of O or A and slight decrease in B) in the blood group diagram of two poliomyelitis series, separated by over 10 years, is noteworthy as is the uniformity in the maintenance of normal distribution frequencies in several American urban centers over a similar and even longer period of time.

TABLE V

Blood Group Distribution in Two Poliomyelitis Series (New York) Compared with Blood Group Distribution in Eight Normal Series (New York, Boston, Detroit, Milwaukee)

Author	Locality	Year	Cases	Number	O %	A %	B %	AB %
Jungeblut and Smith	Greater New York	1931	Paralytic Poliomyelitis	236	46.6	38.1	10.6	4.7
Jungeblut, Karowe and Braham	Greater New York	1944/45	Paralytic Poliomyelitis	220	42.7	43.2	10.9	3.2
Tiber	Greater New York	1928	Normal	10,000	45.6	36.4	13.5	4.5
Jungeblut and Smith	Greater New York	1931	Normal	1,000	45.6	35.7	14.0	4.7
Jungeblut, Karowe and Braham	Greater New York	1942/45	Normal	20,211	45.5	36.4	13.6	4.5
Wiener	Greater New York	1933/43	Normal	1,077	41.7	37.9	13.9	6.6
Jones	Boston	1921	Normal	197	47.2	35.5	13.7	3.5
Culpepper and Ableson	Detroit	1921	Normal	5,000	44.4	36.0	14.2	5.1
Seeger and Schaeffer	Milwaukee	1930/33	Normal	489	42.1	36.2	13.9	7.8
Graves	St. Louis	1934	Normal	281	40.9	39.9	13.5	5.7

## DISCUSSION

The data reported in this paper tally with previously published figures in showing that individuals with blood group B occur "significantly" \* less often among paralytic poliomyelitis patients than among comparable normal controls. The higher frequency of blood group A in our paralytic series.

\* Whenever the term "significant" is used in the text it is meant to imply that the difference referred to is "statistically significant" as determined by the usual tests designed to exclude the influence of chance. It must be emphasized, however, that very small differences may attain statistical significance when based on a sufficient number of cases, although they may be of no particular "practical significance" in serving to explain certain phenomena.

We are greatly indebted to Dr. John W. Fertig and Miss Lillian Elvebach of the School of Public Health of the Faculty of Medicine, Columbia University, for their co-

however, is at variance with the bulk of the published material which shows a "significantly" higher percentage for blood group O. The apparent discrepancy may be partly resolved by the fact that the increase in blood group A in our poliomyelitis series is produced by a "significant" and selective elevation in the absolute and relative frequency of subgroup  $A_2$ , whereas the figures for subgroup  $A_1$  remain unchanged. In this respect our observations are in complete harmony with those of Kleinschmidt.<sup>11</sup> The slight predominance of either blood group O or  $A_2$ , as the case may be, finds a simple and rational explanation if one accepts Thomsen's<sup>18</sup> theory that the so-called agglutinin  $\alpha_2$  is really an agglutinin directed specifically against O red cells. Furthermore, the fact that  $A_2$  individuals are preponderantly heterozygous—with the genotype  $A_2O$ <sup>19</sup>—lends additional support not only to Thomsen's theory but may also provide an understanding for the apparently more frequent association of the phenotypes O and  $A_2$  with the group of paralytic patients. A new finding which has emerged from this work and which will require further investigation before it can be generally accepted is our observation that the percentage of the "Non-secretor" type in paralytic poliomyelitis was "significantly" above the figures considered normal at the present time. Since the inability to secrete blood group substance peripherally represents a minority (or deficiency) trait among normal individuals, considerable interest attaches to its seemingly increased occurrence in patients of a disease as selective as poliomyelitis.

In conclusion it may be said that paralytic poliomyelitis selects individuals with blood groups O or  $A_2$  and "Non-secretor" types somewhat *more* frequently and, vice versa, individuals with blood group B and "Secretor" types somewhat *less* frequently than these groups occur in the normal populations. This fact does not, by itself, bring the problem of predisposition to the disease any nearer to a practical solution. If it is true that both endogenous and exogenous factors operate in conjunction to precipitate the paralytic attack, consideration of endogenous dissimilarities alone cannot possibly measure more than a fraction of the components that condition the state of physiological equilibrium. Hence, the resulting indices of resistance or susceptibility, at best, are only relative and far from absolute. More important yet, since

operation in scrutinizing our data as to their statistical significance. Their conclusions may be summarized briefly as follows:

1. None of the individual paralytic poliomyelitis series shows a statistically significant difference in the frequency of occurrence of any single blood group as compared with the corresponding control series. However, taking into consideration all of the series of paralytic cases against their corresponding controls, in view of the consistency of the difference, there may be said to be a statistically significant decrease of Blood Group B and an increase of O as compared to the controls. It must be emphasized, however, that the small differences attain significance only because of their consistency and because of the very large numbers in some of the groups.

2. The  $A_1/A_2$  ratio of the two paralytic poliomyelitis series (Kleinschmidt; Jungeblut, Karowe, and Braham) differs significantly from the corresponding normal control figures.

3. The increase of "Non-secretors" in the paralytic poliomyelitis series is significant when compared with the normal figures.

4. The probability of obtaining the difference in question by chance alone is, in each case, less than one in a hundred.



the investigation of blood groups is limited to phenotypes, no information is gained on the genetic mechanisms involved in the genotype of the individual. However, our data serve to emphasize again the importance of hereditary influences as the major determinants for the crippling caused by the disease. This viewpoint has been repeatedly discussed by competent observers. Evidence for the existence of an autosomal recessive gene for susceptibility to paralytic involvement was recently adduced by Addair and Snyder.<sup>20</sup> Why the genetic transmission of such factor or factors should be associated with a given group gene and not with another is a question that cannot be discussed at present without the risk of hazardous speculation. Further studies on blood grouping in families in which multiple cases of poliomyelitis have occurred, with closer examination of the respective pedigrees, would probably throw more light on this problem.

### SUMMARY AND CONCLUSIONS

1. A survey of the literature on blood grouping in poliomyelitis shows essential agreement that the incidence of blood group B is slightly decreased and that of blood group O slightly increased in paralytic patients as compared with corresponding normal control populations.

2. Blood group determinations on a series of 220 paralytic poliomyelitis patients from Greater New York during 1944/45 confirmed the shortage of blood group B but indicated a slight increase of blood group A over the normal control figures. This increased percentage of blood group A was caused selectively by elevation of the absolute and relative frequency of subgroup  $A_2$ , whereas the figures for subgroup  $A_1$  remained essentially unchanged.

3. The fact that in the present study blood group  $A_2$  predominated among the poliomyelitis patients whereas in most other studies blood group O was in excess, may be explained on the basis of Thomsen's theory that the so-called agglutinin  $\alpha_2$  is specifically directed against O cells.

4. The poliomyelitis series showed a distribution of the Rh<sub>0</sub> factor which differed very little from the normal value.

5. The series of poliomyelitis patients showed an increased occurrence of the "Non-secretor" type against normal control figures.

6. The available data suggest that individuals with blood groups O,  $A_2$  and "Non-secretor" types tend to suffer paralytic involvement in poliomyelitis more often than one would expect from the normal distribution figures for these groups; vice versa, individuals with blood groups B and "Secretor" types seem to be somewhat less frequently thus affected as compared with the distribution of these groups in normal populations. The frequency of occurrence of blood group  $A_1$  in paralytic patients appears to be essentially the same as found in normal controls.

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# RIGHT VENTRICULAR AND RIGHT AURICULAR HYPERTROPHY OF OBSCURE ORIGIN\*

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IN every collection of a large number of patients with heart disease there are a few examples of cardiac enlargement and cardiac failure in which there are no clues to the nature of the underlying pathologic process. White<sup>1</sup> has stated that about one such case is encountered yearly at the Massachusetts General Hospital. Three were reported from that hospital in 1942.<sup>2</sup> Ordinarily when a patient with heart disease of obscure origin is encountered an attempt is made to fit him into one of the well recognized etiologic categories of heart disease, but there is a large group of poorly recognized disorders of the heart and aorta which merits our attention and into which many of these confusing cases may fall.<sup>3</sup> The majority of patients with so-called idiopathic cardiac hypertrophy have shown enlargement of the left ventricle alone or diffuse cardiac enlargement. Two cases of cardiac hypertrophy and congestive failure of uncertain etiology which exhibited unusual features have recently been observed in this clinic. One patient proved to have hypertrophy confined to the right side of the heart associated with dilatation of the pulmonary arterial tree; the other displayed enlargement and dilatation of the right auricle and moderate hypertrophy of the left ventricle.

## CASE REPORTS

*Case 1.* J. P., a 14-year-old schoolgirl, was first seen in the clinic on August 21, 1944. She complained of repeated hemoptyses. In May 1944, she filled a handkerchief with bright, red blood. The following morning she coughed up a small dark clot of blood. Two other small hemorrhages occurred in the month prior to the examination.

When she was an infant the family physician said her heart was "weak." On two occasions the question of some cardiac abnormality was raised during physical examinations at school. For one year she had experienced dyspnea and dizziness when walking up an incline or running. When she played baseball, she had developed the practice of having one of her playmates run the bases for her. Cyanosis had not been noted at birth nor subsequently. There was no other history of cardiac symptoms and no rheumatic manifestations had been noted. The past history and family history were not significant in other respects.

*Physical Examination:* The patient was a well-developed girl who appeared to be in good health. There was some fullness in the region of the thyroid gland but no abnormal pulsations nor dilated vessels were present in the neck. The lungs were clear. The left precordial area displayed a diffuse systolic heaving which was particularly prominent in the second and third intercostal spaces. The heart was slightly enlarged. Along the left sternal margin in the region of the systolic pulsation there

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was a moderately loud, blowing, systolic murmur and a conspicuously accentuated pulmonic second sound. In the same area there was a brief, faint, early diastolic sound. The systolic murmur was transmitted toward the apex. The blood pressure was 118 mm. Hg systolic and 92 mm. diastolic. There was no cyanosis or clubbing of the fingers or toes. The remainder of the examination was negative.

*Laboratory Data:* The hemoglobin was 16.6 gm. (106 per cent). The blood Kahn reaction was negative. Fluoroscopic examination of the heart disclosed hypoplasia of the aorta and dilatation of the undivided portion of the pulmonary artery. The

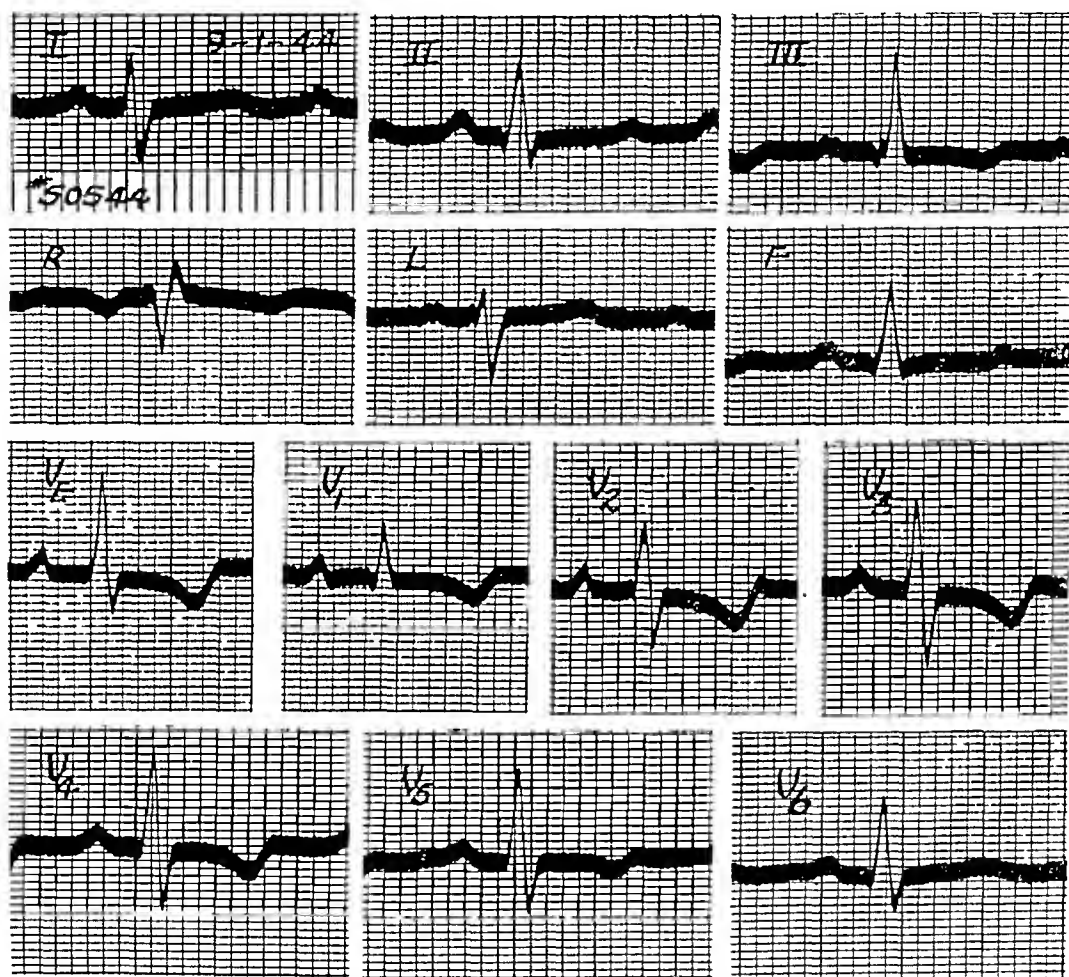


FIG. 1. Case 1. September 1, 1944. Standard leads show slight right axis deviation. The precordial leads display prominent, late R-waves in Leads  $V_1$  and  $V_2$ , and inverted T-waves in all leads except  $V_6$ . These changes suggest moderate right ventricular hypertrophy.

retrocardiac space was clear throughout. The frontal plane area of the cardiac silhouette was 29 per cent above the predicted normal by both orthodiagraphic and teleoroentgenographic methods. The standard and unipolar electrocardiograms display slight right axis deviation and rather broad, notched P-waves in all leads (figure 1). The precordial leads exhibit prominent, late R-waves and absent S deflections in lead  $V_1$  and inverted T-waves in all of the records except lead  $V_6$ . These findings are suggestive of moderate right ventricular hypertrophy.

*Subsequent Course and Second Admission:* The patient was not seen again until October 11, 1944 when she was admitted in extremis. One week earlier minimal

generalized edema, and pain in the abdomen, back and right shoulder had appeared. For two or three nights she had been restless and unable to sleep well. She continued to attend school until the day prior to admission when she developed severe dyspnea. Soon thereafter the edema of the ankles and face became more pronounced.

*Physical Examination:* The patient was orthopneic and very cyanotic. There was moderate edema of the lower extremities and face. The heart rate was 120 per minute and a gallop rhythm was heard. Auscultation was unsatisfactory but a loud, harsh systolic murmur was thought to be present over the entire precordium. The patient died 20 minutes after admission.

*Postmortem Examination* (Performed by Dr. Martin R. Sutler, Jr.): The heart appeared to be in an abnormal position when inspected in situ. No part of the left ventricle could be seen; the anterior aspect consisted of the right atrium and right ventricle. The heart weighed 344 gm. (average normal at this age is 157.4 gm.<sup>4</sup>). The right ventricular wall was 7 mm. in thickness; the left ventricular wall was 8 mm. in thickness. The right atrium was moderately dilated. The leaflets of all valves were normal and the interatrial and interventricular septa were intact. The circumferences of the valves were: mitral, 80 mm.; tricuspid, 112 mm.; aortic, 55 mm.; pulmonic, 75 mm. The coronary arteries were normal. The main pulmonary artery was a little greater in circumference than normal. The pulmonary arteries throughout, down to the smallest branch, appeared to be dilated. There was an early infarction of the lower two-thirds of the left lower lobe apparently resulting from a rider's embolus extending into the main arterial branch to the lower lobe and straddling into a small radicle from this branch. There were no abnormalities of the thoracic aorta and the ductus arteriosus was obliterated. There was moderate ascites and slight pleural and pericardial effusion.

Microscopic examination of the heart disclosed muscle fibers in a patchy distribution which appeared somewhat larger than normal. There were petechial hemorrhages in the sub-epicardial fat and non-lipoidal vacuolar changes in the subendocardium. The aorta exhibited marked hypoplasia. The lungs displayed an intense, acute exacerbation of chronic passive congestion, hemorrhage into alveolar spaces and severe catarrhal bronchitis. There was chronic passive congestion of the liver and spleen.

*Case 2.* H. C., a 21-year-old bookkeeper, entered the University Hospital on June 14, 1944, complaining of dyspnea and ankle edema. She had been aware of some dyspnea on exertion all her life. An episode of ankle edema lasting two or three days occurred in December 1943. In January 1944, she had fever and a productive cough for three or four days. Ankle edema reappeared in April 1944, and ascites developed soon thereafter. Early in May 1944, she was in hospital for four weeks and was considerably relieved by digitalis and diuretics. Roentgenographic examination was said to have revealed cardiac enlargement and earlier films made in 1937 were found to display similar changes in the heart. One week prior to admission her symptoms recurred despite continued bed rest. Her diet had been adequate. She had minimal tuberculosis at age 13 which required treatment in a sanatorium for seven months. The past history and family history were not significant in other respects.

*Physical Examination:* The patient was normally developed and in a good state of nutrition. She was severely dyspneic and moderately cyanotic. There was a persistent slightly productive cough. There were occasional unusually prominent, systolic venous pulsations in the neck; these were found to correspond to periods of atrio-ventricular nodal rhythm. The heart was very much enlarged and a forceful apex impulse was located in the mid-axillary line at the fifth interspace. The cardiac sounds were loud and the pulmonic second sound was conspicuously accentuated. No significant murmurs were heard. The blood pressure was 124 mm. Hg systolic and 80 diastolic. Numerous râles were present over the lower portions of both posterior lung fields. A smooth, firm, tender liver extended to the level of the right iliac crest and

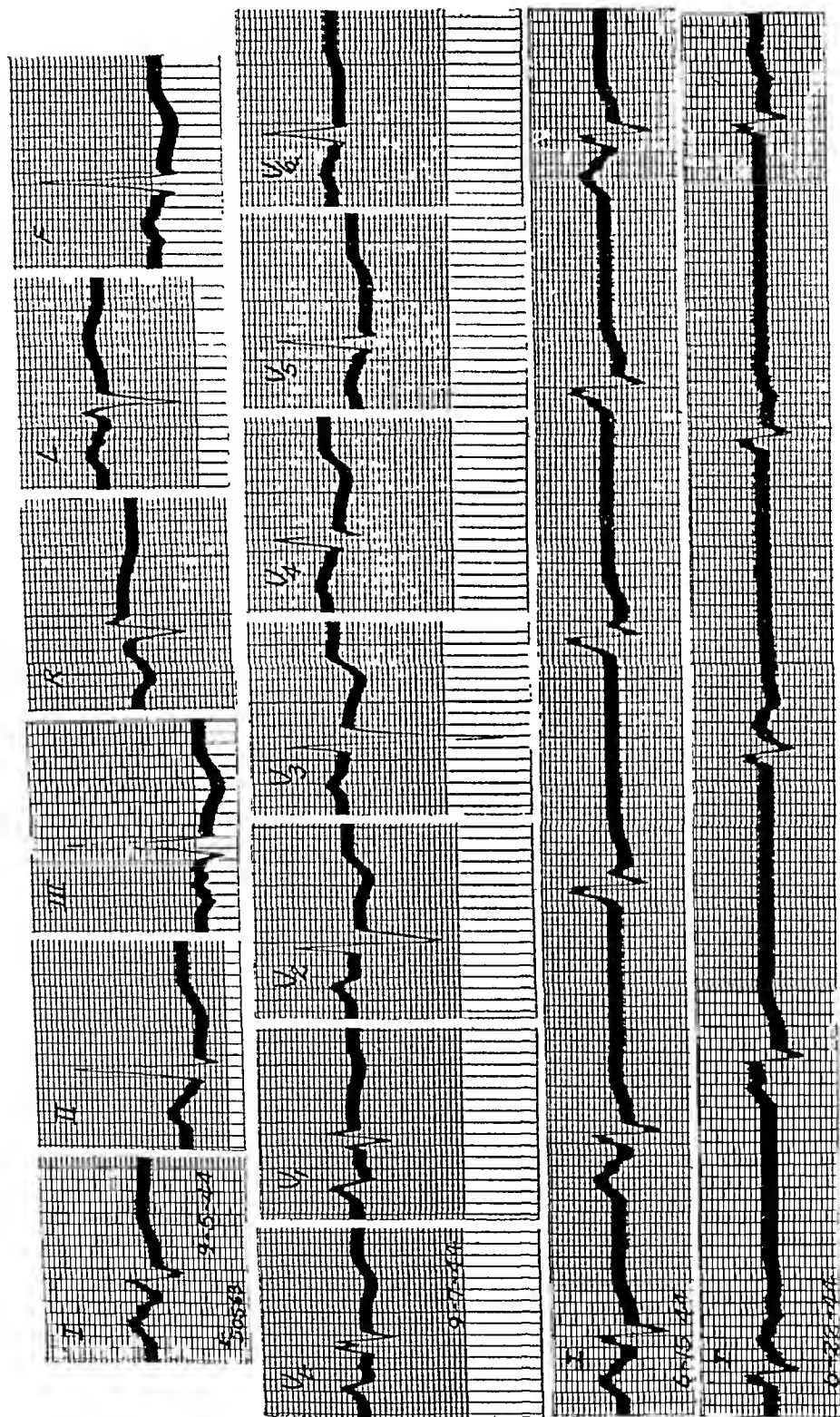


FIG. 2. Case 2. Standard leads on September 5, 1944, show slight right axis deviation and unusually broad, notched P-waves. Precordial leads on September 9 display prominent R' deflections in Lead V<sub>1</sub>. Electrocardiograms suggest auricular hypertrophy and incomplete right bundle branch block. Inverted T-waves in Leads II, III, and precordial leads are probably due in part to digitalis. Records on June 15 and 22 show transient atrio-ventricular nodal rhythm.

displayed questionable pulsation. There was moderate edema of the legs and the sacral region.

*Laboratory Data:* Albuminuria of slight degree was found from time to time but the urine was not otherwise abnormal. The hemoglobin ranged from 92 per cent to 115 per cent and there was a moderate leukocytosis (14,600) on admission; the blood was normal in other respects. Examinations of the sputum, stool, serum proteins and blood chlorides and cultures of the blood and sputum were negative. The blood Kahn reaction was negative. Several roentgenographic examinations of the thorax revealed considerable cardiac enlargement, broadening of the waist of the heart, flattening of the cardiophrenic angle bilaterally, and reduction of the retrocardiac space. Fluoroscopic observation disclosed no pulsations along the lower borders of the heart and marked diminution of the pulsations of the upper borders.

*Electrocardiograms:* The standard and unipolar limb leads on June 15, 1944, showed moderate right axis deviation with very broad, large, notched P-waves in all leads and unusually large R-waves in Leads II and III. The T-waves were flat in Lead I and inverted in Leads II and III; this was attributed, at least in part, to digitalis. Transient atrio-ventricular rhythm was also present. Similar electrocardiograms were recorded on June 16 and 26, September 5, and October 4. Records taken on June 22 displayed a transient low atrio-ventricular rhythm with marked variations in the location of the pacemaker, and occasional probably reëntrant beats. Precordial leads taken on September 7 exhibit prominent late R' deflections and unusually large P-waves in Lead V<sub>1</sub>, notched R-waves in Lead V<sub>E</sub>, inverted T-waves in all leads, and unusually large QRS deflections, particularly in Leads V<sub>2</sub> and V<sub>3</sub> (figure 2). These records suggest auricular and ventricular hypertrophy and probable incomplete right bundle branch block but they are not characteristic of preponderant right or left ventricular hypertrophy.

*Hospital Course:* The patient was treated for congestive heart failure in the usual fashion. She was in an oxygen tent continuously for the first two months in the hospital. Her course was complicated by a transient left facial paralysis on June 18, and bronchopneumonia on June 22. She made slow, gradual improvement and in September she was permitted out of bed for short periods. Shortly thereafter manifestations of congestive heart failure reappeared, grew rapidly worse, and she died on October 7, 1944.

*Postmortem Examination* (Performed by Dr. Martin R. Sutler, Jr.): The heart weighed 432.5 gm. The left ventricular wall was 15 mm. thick and appeared hypertrophied. The right ventricular wall measured 4 mm. in thickness. The right atrium was greatly enlarged and dilated. The left atrium displayed a calcified, sclerotic plaque 3 by 2 cm. in size in the endocardial and subendocardial tissue of its left posterolateral wall. The coronary sinus opening into the right atrium appeared very large at its mouth and dilated throughout its course. All the valves were normal and their circumferences were: mitral, 110 mm.; tricuspid, 126 mm.; aortic, 54 mm.; and pulmonary, 60 mm. None of the common congenital cardiovascular anomalies were present. There was acute exacerbation of chronic passive congestion of the lungs. The pulmonary vessels appeared normal. There was chronic passive congestion of the liver and spleen and a small effusion in each pleural space.

Microscopic examination disclosed moderate hypertrophy of the myocardium with an increase in stroma and an anomalous pattern with interlacing of the heart muscle fibers, especially in the left ventricle. The coronary arteries were negative. The pulmonary arterial and arteriolar walls were not thickened. Congestion of all viscera was present.

#### COMMENT

As our knowledge increases more and more, cases now classified as idiopathic cardiac hypertrophy will no doubt be placed in definite etiological



categories. The development of the sphygmomanometer made possible the separation of cases of hypertensive heart disease from the idiopathic group and the recognition of abnormal glycogen storage permitted the identification of cases of von Gierke's disease. It is desirable that each example of cardiac enlargement of uncertain origin be carefully investigated in the hope that some clue to the nature of the pathological process be uncovered. In the majority of the reported cases of cardiac hypertrophy of obscure etiology the patients have been infants or children. In 1942, Weisman<sup>5</sup> found 70 cases of this disorder in children in a survey of the literature which included the earlier reviews of Kugel and Stoloff<sup>4</sup> and Mahon.<sup>6</sup> In this large series, 70 per cent of the patients were under one year and none were over nine years of age. Reports of idiopathic cardiac hypertrophy in adults have, for the most part, concerned isolated examples, but Levy and Von Glahn<sup>7</sup> reviewed 14 cases from the literature and reported 10 of their own. Kaplan, Clark, and de la Chapelle<sup>8</sup> were able to find 11 cases at the Bellevue Hospital during a three year period. The criteria which have led different writers to consider cases of cardiac hypertrophy as idiopathic or unclassifiable, on an etiologic basis, have varied considerably. The reason for this is that there are still differences of opinion as to just what structural lesions disclosed by postmortem examination can be regarded as adequately accounting for this change in the heart muscle. In some of the reported instances the observations made have not been sufficiently extensive to exclude all the known causes of cardiac hypertrophy.

The two cases which form the basis of this report showed involvement of the right heart, particularly, and the predominant symptoms were those of right-sided cardiac failure. The incidence of cor pulmonale and its numerous underlying causes have been discussed in the publications of Griggs, et al.,<sup>9</sup> Scott and Garvin,<sup>10</sup> and von Bonsdorff.<sup>11</sup> It is necessary here only to point out that our patients showed no evidence of primary pulmonary disease or distortion of the thoracic cage<sup>12, 13</sup> which could account for the cardiac involvement. These two patients presented many symptoms and signs suggestive of pulmonary disease with pulmonary arterial hypertension, particularly cough, dyspnea, cyanosis, hemoptysis, systolic pulsation along the upper left sternal margin, an accentuated pulmonic second sound, and electrocardiographic signs suggestive of right ventricular hypertrophy. The various etiologic factors which may be responsible for this disorder have been reviewed by Brenner<sup>14</sup> and Balboni<sup>15</sup> and subdivided by the latter into primary pulmonary arteriosclerosis (obliterating endarteritis of small arterioles) and secondary pulmonary arteriosclerosis (atherosclerosis of large arteries resulting from conditions producing an elevated arterial pressure in the pulmonary arteries). Our first case revealed only dilatation of all the pulmonary arteries rather than narrowing of the lumina or thickening of the arterial walls with associated dilatation of the type described by Brenner.<sup>14</sup> Our second case exhibited no abnormalities of the pulmonary arteries.

Idiopathic hypertrophy of the right heart has been described only rarely.



A survey of the literature has been made and we have considered the hypertrophy idiopathic only when: (a) the clinical, pathological, and microscopic examinations were adequate to exclude all known causes of right ventricular hypertrophy; (b) the examination of the heart at autopsy confirmed the diagnosis of this cardiac abnormality; and (c) there were no congenital cardiovascular anomalies other than the right heart hypertrophy itself. We were able to find six reported cases which met these criteria and are considered as acceptable (table 1). The two cases described in this report are added to this group, although it must be pointed out that in Case 2, the involvement was most striking in the right auricle and that some hypertrophy of the left ventricle was also present. In addition, we have found six reported cases which are considered as probably acceptable (table 2). The authors who published these were of the opinion that the minor pathological changes in the lungs were inadequate to account for the cardiac enlargement. Two of the patients showed minor pulmonary arteriolar narrowing; one exhibited sclerotic changes in the larger pulmonary arteries; one had purulent bronchitis and bronchiectasis; another displayed emphysema; a microscopic examination of the lungs was not made in the case of the sixth patient in this group. The cases reported by Hueter<sup>23</sup> and Zuber<sup>24</sup> have been included as examples of right ventricular hypertrophy of unknown origin in other studies of this subject; they are not included as such in this review because a patent ductus arteriosus was present in each of them and in one the foramen ovale was open<sup>23</sup> in addition.

All of the reports have not been sufficiently detailed to make possible an extensive analysis of the symptoms manifested by the various patients, but a study of tables 1 and 2 will give information which may have value in the clinical consideration of possible examples of idiopathic right cardiac hypertrophy. There were four males and 10 females. The age range was 10 months to 73 years. Dyspnea, appearing initially on exertion but later at rest, cyanosis, cough, ascites and edema were the most common, important complaints. Congestive failure in these patients was of the type generally classified as right-sided heart failure; ascites, edema, and hepatic and venous engorgement predominated over the signs of respiratory embarrassment. In some patients, when heart failure occurred, it progressed to a fatal termination in a few days; other patients survived for several months or years despite repeated episodes of decompensation. The most frequent and most significant abnormal physical signs were a systolic murmur and a prominent systolic pulsation in the pulmonic area, and an accentuated, often palpable, second sound in the same zone. These signs were particularly striking in our Case 1. Clubbing of the fingers and toes and polycythemia occurred infrequently and were not as striking as in most patients with cyanotic congenital heart disease. The death of 12 of the 14 patients was due to cardiac failure; of the two remaining patients one died of bronchopneumonia and the other of suppurative pyelophlebitis. Roentgenographic observations usually disclosed signs of right ventricular hypertrophy, dilatation of the pul-

TABLE I  
Acceptable Cases

No.	Author	Sex	Age	Clinical Features	Pathology	Electrocardiograms
1	Howland <sup>16</sup>	F	2½	Pain in heart, syncope, cyanosis, and anorexia.	Heart weighed 120 gm. R.V. wall 6.6 mm.; L.V. wall 6.0 mm. Hypertrophy and dilatation of right heart. Pulmonary artery dilated. Walls of pulmonary vessels thin and delicate.	None reported.
2	Oppenheimer <sup>17</sup>	M	46	Cough, dyspnea, accentuated pulmonic second sound. Death due to suppurative pyelophlebitis.	Hypertrophied right ventricle; small left ventricle. Huge pulmonary artery and main branches with dilatation almost to pleural surface. Some arteriosclerotic plaques. Slight intimal thickening of arterioles.	Right axis deviation; inverted T <sub>2</sub> and T <sub>3</sub> .
3	Oppenheimer <sup>17</sup>	F	60	Cyanosis, dyspnea, moderate polycythemia. Died of acute congestive heart failure of three days' duration.	Marked right ventricular hypertrophy; small left ventricle and rather small aorta. Huge dilatation of pulmonary artery and dilatation of all the pulmonary arteries.	Right axis deviation; inverted T <sub>2</sub> and T <sub>3</sub> .
4	De Navasquez, et al. <sup>18</sup>	M	30	Attacks of syncope, cough, insomnia, cyanosis, and slight dyspnea for 1 year.	Heart weighed 530 gm. L/R ratio 0.87. Dilatation of pulmonary artery throughout its branches as far as periphery of lung. Fatty atheroma in streaks and plaques and irregular thickening of intima in larger branches, questionable medial hypertrophy in smaller branches.	Right axis deviation with inversion of T <sub>2</sub> and T <sub>3</sub> ; depression of RS-T segment.

TABLE I—Continued

No.	Author	Sex	Age	Clinical Features	Pathology	Electrocardiograms
5	De Navasquez, et al. <sup>18</sup>	M	49	Dyspnea, clubbing, cyanosis, and polycythemia for 3 or 4 years.	Heart weighed 630 gm. L/R ratio 0.80. Pulmonary artery uniformly dilated as far as first division. Second branches conspicuous and show patchy fatty atheroma. Remaining branches normal.	Marked right axis deviation with low voltage and flattening of T <sub>3</sub> .
6	East <sup>19</sup>	F	24	Attacks of right ventricular failure for 6 years. Systolic pulsation and very loud second sound in pulmonic area.	Heart weighed 391 gm. Right ventricle—210 gm. Right auricle much distended. Catarrhal cells in pulmonary alveoli, slight hypertrophy of arteriolar muscle coats. No change in intima.	None reported.
7	Rosenbaum	F	14	Hemoptysis and dyspnea on exertion for 5 months. Rapid, terminal congestive heart failure. Systolic pulsation and murmur, palpable accentuated second sound in pulmonic area.	Heart weighed 344 gm. Marked right ventricular hypertrophy and right auricular dilatation. Dilatation of pulmonary artery and all its branches. Pulmonary arterioles normal. Aorta hypoplastic.	Slight right axis deviation, broad P waves in all leads. Precordial leads suggestive of right ventricular hypertrophy.
8	Rosenbaum	F	21	Dyspnea on exertion all her life. Progressive ankle edema, ascites, cyanosis and congestive heart failure for 14 mos. Accentuated pulmonic second sound. Slight polycythemia.	Heart weighed 432.5 gm. Tremendous enlargement and dilatation of right atrium. Moderate left ventricular hypertrophy. Pulmonary vessels normal.	Moderate right axis deviation with broad P waves in all leads and inverted T <sub>2</sub> and T <sub>3</sub> . Chest leads suggest incomplete right bundle branch block.

monary arteries and unusual prominence of the right ventricular conus. The electrocardiograms uniformly displayed right axis deviation. The precordial electrocardiograms in our Case 1 confirmed the diagnosis of right ventricular hypertrophy. In Case 2, the electrocardiograms suggested auricular hypertrophy and incomplete right bundle branch block, but were not characteristic of either right or left ventricular hypertrophy; transient atrio-ventricular nodal rhythm also occurred in this instance.

Dilatation of the pulmonary arteries was described in all but two of the 8 cases listed in table 1 and in four of the six cases in table 2. As in Case 1, in many instances this dilatation extended to the very periphery of the lungs. Congenital widening or aneurysmal dilatation of the main stem of the pulmonary artery or its branches as a primary condition is quite rare. Costa<sup>25</sup> reviewed the literature on this subject extensively and found that pulmonary arterial aneurysms were associated with other congenital cardiovascular anomalies in 47 per cent of the cases; luetic arteritis (about 20 per cent), mycotic-embolic arteritis (6 per cent), rheumatic heart disease, pulmonary disease of various types, phlebitis of the pulmonary veins, or trauma accounted for nearly all of the other examples of this disorder. Costa felt that this was unexpected in view of an earlier study in which he had discovered an anomalous hypoplastic histological structure in the pulmonary arterial walls in 14 per cent of 210 cases.<sup>26</sup> Clarke, et al.,<sup>20</sup> Abbott,<sup>27</sup> D'Aunoy and von Hamm,<sup>28</sup> and Scott<sup>29</sup> have all been similarly impressed by the infrequency of primary pulmonary arterial dilatation. It is noteworthy that in Costa's group of 73 cases of pulmonary arterial aneurysm, 71 per cent displayed hypertrophy confined to the right ventricle and about 35 per cent exhibited dilatation of the ramifications of the pulmonary arterial system.<sup>25</sup>

The relationship between dilatation of the pulmonary arteries and right cardiac hypertrophy such as was present in our Case 1 and such as was observed in the similar cases listed in tables 1 and 2 is not clear. Right ventricular enlargement has been a common finding in the recent reports of pulmonary aneurysm.<sup>28, 29, 30</sup> Inasmuch as aortic aneurysms uncomplicated by aortic valvular disease are rarely responsible for left ventricular hypertrophy, it would be surprising if pulmonary aneurysms should, of themselves, give rise to right ventricular hypertrophy. The factor of relative pulmonic insufficiency may be operative in patients with more diffuse pulmonary arterial widening; the presence of pulmonary diastolic murmurs in some cases suggests that this is the case.<sup>17</sup> Brenner<sup>14</sup> has expressed the opinion that in primary pulmonary arteriosclerosis "the vascular lesions are rarely extensive enough in themselves to embarrass the pulmonary circulation seriously and more probably they and the hypertrophy of the right side of the heart are manifestations of some common unknown cause." Here, too, it may well be that the right cardiac enlargement and the pulmonary arterial dilatation are related only insofar as they have a common etiological background.

TABLE II  
Probably Acceptable Cases

No.	Author	Sex	Age	Clinical Features	Pathology	Electrocardiograms
1	Clarke, et al. <sup>20</sup>	F	10 mos.	Numerous attacks of dyspnea and cyanosis. Progressive severe cough. Died from bronchopneumonia.	Dilatation and hypertrophy of right ventricle. Pulmonary artery dilated above valve and throughout its branches. Vessel walls normal. Pulverulent bronchitis, bronchiectasis with peribronchial fibrosis.	None reported.
2	Ulrich <sup>21</sup>	F	27	Weakness on exertion for 12 years. Hoarseness and hemoptysis for 3 years. Dyspnea, edema, cyanosis, uterine bleeding, and slight polycythemia. Mitral murmur.	Heart weighed 360 gm. Great dilatation and moderate hypertrophy of right auricle and right ventricle. Pulmonary artery dilated. Sclerotic thickening of larger branches of pulmonary artery and dilatation of some of the midesized branches. No sclerosis of arterioles.	Right ventricular preponderance.
3	De Navasquez, et al. <sup>18</sup>	M	55	Dyspnea, cough, ascites, and edema. Repeated attacks of short duration.	Heart weighed 650 gm. L/R ratio 0.84. Great hypertrophy of right ventricle; other chambers normal. Pulmonary artery showed dilatation and slight atheroma in streaks in main branch. Pulmonary arteries 2 to 10 mm. in size showed crescentic thickening of intima. Other vessels normal.	None reported.

TABLE II—Continued

No.	Author	Sex	Age	Clinical Features	Pathology	Electrocardiograms
4	East <sup>19</sup>	F	31	Dyspnea and cyanosis for years. Ascites, edema and venous engorgement prior to death. Systolic murmur and pulsation, accentuated and palpable second sound in pulmonic area.	Heart weighed 415 gm. Right ventricle greatly enlarged, wall 5 mm. thick; left ventricle normal, wall 7 mm. thick. Pulmonary artery large and prominent. No macroscopic abnormality of pulmonary vessels; no sections reported.	Right axis deviation with diphasic T <sub>2</sub> and inverted T <sub>3</sub> .
5	East <sup>19</sup>	F	31	Increasing dyspnea, venous engorgement, cyanosis, edema, and right heart failure. Systolic pulsation and accentuated, palpable second sound in pulmonic area.	Heart weighed 372 gm. Massive hypertrophy of right ventricle; left ventricle normal. Right auricle engorged. Pulmonary artery large. Muscle coats of smaller arterioles slightly thickened and a few smallest arterioles obliterated.	Right axis deviation with inverted T <sub>3</sub> .
6	Armstrong <sup>22</sup>	F	73	Dyspnea, ascites, ankle edema, and cyanosis for 4 years. Died suddenly. Systolic murmur and accentuated second sound in pulmonic area.	Heart weighed 425 gm. Great hypertrophy of right ventricle and auricle. Severe atheroma in pulmonary arteries. Pulmonary arterioles normal. Emphysematous bullae and fine, even pulmonary emphysema.	Right ventricular preponderance.

TABLE III

## Etiological Hypotheses for Idiopathic Cardiac Hypertrophy\*

- A. Congenital Imperfections or Anomalies of the Cardiovascular or Pulmonary Arterial Systems.
    1. Congenital narrowing of the capillary bed (Emerson<sup>31</sup>).
    2. Unrecognized arterio-venous aneurysm (Powers, et al.<sup>32</sup>).
    3. Congenital narrowing or excessive size of aorta (Fraentzel<sup>33</sup>).
    4. Anomalies of the coronary arteries (Abrikossoff,<sup>34</sup> Carrington and Krumbhaar<sup>35</sup>).
    5. Underdevelopment of the coronary arteries with chronic myocardial ischemia (Weiss<sup>3</sup>).
    6. Congenital medial sclerosis of the coronary arteries (Kissane and Fidler<sup>36</sup>).
    7. Imperfection of the stuff of the pulmonary artery (Schwalbe,<sup>37</sup> Clarke, et al.<sup>20</sup> or loss of elastic tissue of the pulmonary artery with overload of the heart (Ulrich<sup>21</sup>).
    8. Excessive resistance in the pulmonary system (Fraentzel<sup>33</sup>).
    9. Disorders of the cardiac nervous system (Fraentzel<sup>33</sup>).
    10. Constitutional basis, particularly hypertension in the parents (Katz,<sup>38</sup> Mussliner<sup>39</sup>).
    11. Inherited tendency to cardiac anomalies (Sprague, et al.,<sup>40</sup> Clarke, et al.<sup>20</sup>).
  - B. Abnormal Infiltrations of the Heart.
    1. Non-suppurative myocardial infiltration with dilatation and hypertrophy (Kugel and Stoloff,<sup>4</sup> Kugel<sup>41</sup>).
    2. End stages of glycogenesis (Antopol, et al.<sup>42</sup>) or cardiomegalia glycogenica circumscripta (Van Creveld and Van der Linde<sup>43</sup>).
    3. Diffuse rhabdomyoma (Virchow<sup>44</sup>).
    4. Fatty heart (Fraentzel<sup>33</sup>).
    5. Round cell infiltration causing fatty degeneration and atrophy (Riesenfeld<sup>45</sup>).
    6. Endocardial fibrosis (Mahon,<sup>6</sup> Weisman<sup>5</sup>).
    7. Synechia of the pericardium (Michaud<sup>46</sup>).
  - C. Infections.
    1. Respiratory infections of the mother during pregnancy (Weiss<sup>3</sup>).
    2. Respiratory infections of the new-borne (Weiss<sup>3</sup>).
    3. Recurrent myocarditis (Krstulovic,<sup>47</sup> White<sup>2c</sup>).
    4. Effects of pertussis with prolonged coughing (Hauser<sup>48</sup>).
    5. Diphtheritic myocarditis (Fraentzel<sup>33</sup>).
    6. Toxic myocarditis associated with various infections (Fahr and Kuhle,<sup>49</sup> Ceelen<sup>50</sup>).
  - D. Metabolic Disorders.
    1. Obesity (Hamman<sup>51</sup>).
    2. Avitaminosis (Kugel and Stoloff<sup>4</sup>).
    3. Glycogen storage disease (von Gierke,<sup>52</sup> van Creveld<sup>53</sup>).
    4. Excessive alcohol consumption (Michaud,<sup>46</sup> Fraentzel,<sup>33</sup> Blumer<sup>54</sup>).
    5. Hypothyroidism.
    6. Unknown metabolic disorders (Powers, et al.<sup>32</sup>).
  - E. Diseases of Other Organs or Systems.
    1. Disease of the kidney (Fraentzel<sup>33</sup>); scarlatinal nephritis (Michaud<sup>46</sup>).
    2. Anemia of long duration (Michaud<sup>46</sup>).
    3. Hypersecretion (Hedinger<sup>55</sup>) or hyposcretion (Michaud<sup>46</sup>) of chromaffin tissue.
    4. Status thymicolymphaticus (Henoch,<sup>56</sup> Riesenfeld,<sup>45</sup> Steiner and Bogin<sup>57</sup>).
  - F. Transient Overloading of the Heart with Dilatation and Subsequent Hypertrophy (Eyster,<sup>58</sup> Powers, et al.<sup>32</sup>).
1. Antecedent hypertension (Kaplan, et al.<sup>8</sup>).
  2. Allergy (Mahon<sup>6</sup>).
  3. Intrauterine circulatory disturbance present only in fetal life disappearing or becoming unrecognizable at birth (Howland,<sup>18</sup> Simmonds<sup>59</sup>).
  4. Intrauterine fibrosis of lungs with narrowing of capillary field, increasing pulmonary arterial pressure during the first few hours of life (Clarke<sup>20</sup>).
  5. Enlargement of the heart in pregnancy (Fraentzel,<sup>33</sup> Sodeman<sup>60</sup>).

\* Authors cited mention or support the theory in question but are not necessarily the original proponents of that particular hypothesis.

The majority of the hypotheses which have been advanced to account for cardiac hypertrophy of obscure origin have been summarized in table 3. It is outside the scope of this report to discuss the relative merits of these various theories. In individual cases thorough pathological study will exclude many of these postulated factors, particularly those in the group of abnormal myocardial infiltrations. The two patients reported here may be considered examples in which such an exclusion is possible. In other instances, the underlying difficulty may be disclosed by careful investigation of the patient's history or special clinical examinations may be developed in the future which will prove useful in this regard. Such observations are impossible in those cases in which congestive failure appears and terminates fatally in a very short time. One of the explanations of obscure cardiac hypertrophy which seems most plausible is that of overloading of the heart with transient dilatation and subsequent hypertrophy such as Eyster<sup>58</sup> produced in experimental animals. It is conceivable that obscure infections occurring in utero or in infancy may make the heart more susceptible to such transient overloading.

### SUMMARY

Two cases of idiopathic cardiac hypertrophy occurring in young women and terminating fatally with congestive heart failure are described. In one patient the hypertrophy was confined to the right ventricle and auricle and was accompanied by dilatation of the entire pulmonary arterial tree. In the second case the most striking enlargement was found in the right auricle and was associated with moderate left ventricular hypertrophy. The pulmonary vessels were entirely normal in this patient. Careful clinical observations employing new technics such as right heart catheterization may furnish information which will be of importance in solving the problem of the obscure etiology of such cardiac abnormalities.

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## HUMAN GLANDERS: REPORT OF SIX CASES \*

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GLANDERS, primarily an equine disease, occurs naturally in two forms, namely acute or chronic systemic glanders, and cutaneous glanders. In the past, the disease in man has usually been contracted by direct or indirect contact with infected horses. During the past 30 years, however, due to constant testing of horses and eradication of infected animals, this disease entity has been rare in this country. The only case known by the writers to have occurred in the United States in recent years was described by Herold and Erikson<sup>1</sup> in 1938. The disease occurs more frequently in Russia, the Balkans, and parts of Asia and Africa where veterinary control measures are less stringent or non-existent.

A number of accidental infections have been recorded in the past among laboratory workers.<sup>2, 3, 4, 5</sup> The disease as it occurs in man, either from animal sources or as a laboratory infection, has in turn been divided into two clinical forms, namely acute and chronic glanders. Acute glanders is usually rapid in onset and is fatal in 10 to 30 days. It may appear as a bronchopneumonia or a lobar pneumonia, with or without bacteremia, or a generalized pyemia. The prognosis in the severe acute form is usually grave and the mortality has been reported as approaching 100 per cent.<sup>1, 6</sup> Robins<sup>3</sup> points out the possibility that the majority of human glanders cases may have been included in mortality statistics under some other diagnosis. It is further possible that milder or even sub-clinical cases have gone unrecognized and that their inclusion would thereby reduce the over-all mortality in this disease. The diagnosis of glanders has usually been made by culture of blood<sup>7</sup> or external lesions, by serological methods, and by skin tests.<sup>4, 8</sup> Such treatment as has been reported in the literature appears to have been almost completely ineffective.<sup>9</sup> No report has been found on any trial of sulfonamides or antibiotics.

Six cases of glanders are reported herein. These occurred within the space of one year among personnel involved in laboratory research work with *Malleomyces mallei*. Though this organism was not isolated in any of these cases, it may be of interest that four of these individuals (cases 1, 2, 3, and 4) had been handling a strain † of relatively low virulence (M.L.D. for hamsters 20 to 30 organisms) prior to infection. Patients 5 and 6, however, were probably exposed to a more virulent strain ‡ (M.L.D. for

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† Isolated from the lungs of horses in 1942, and obtained from the type collection of the China Natural Epidemic Prevention Bureau.

‡ Strain 3873, isolated from a fatal human case in China in 1944.

hamsters 5 organisms) introduced into the laboratory a short time before the onset of their illness.

Studies have been made on methods of specific laboratory diagnosis,<sup>9, 10</sup> and on chemotherapy of the experimental disease in animals.<sup>11</sup> With regard to the first of these problems, effective methods have been developed for isolation of *M. mallei*. Agglutination and complement fixation tests were studied and one or more titrations were run on each individual working in our laboratory. It was found that normal human sera agglutinated *M. mallei* in dilutions up to 1:320, but did not fix complement.<sup>10</sup> Sera from 35 cases of primary atypical pneumonia, etiology unknown (so-called "virus pneumonia") gave low titered agglutination and negative complement fixation reactions with these antigens. This was an important factor in the differential diagnosis of the six cases under consideration. Agglutinin titers higher than 1:320 were therefore considered diagnostic. Furthermore, a progressive rise in titer in the same individual from negative to 1:320 appeared to be of some significance. The complement fixation test was a less sensitive index, but was more specific. When positive in dilutions of 1:20 or higher, it was diagnostic of infection with *M. mallei*.

Another diagnostic aid was found in a modification of the mallein skin test, permitting its safe use in humans. One-tenth (0.1) c.c. of commercial mallein in a dilution of 1:10,000 was injected intradermally into the skin of the forearm. The test was read at 24 and 48 hours. During the course of the research program, skin tests were performed on a total of 38 normal individuals. Four of these gave a reaction measuring 3 to 7 mm. in diameter after 24 hours, which faded almost completely after 48 hours. It was found that specific positive tests, encountered in the five patients who reacted, reached maximum erythema after about 18 to 24 hours and faded only slightly if at all by the end of 48 hours. The erythema was usually seen to be 10 to 20 mm. in diameter when the test was positive. No systemic symptoms were associated with any of the routine tests. For experimental purposes, however, six months after his recovery, patient 1 was given 0.2 c.c. of a 1:10,000 dilution of commercial mallein intradermally, representing twice the normal skin test dose. During the first 24 hours following injection, he experienced a mild systemic reaction, consisting of fatigue, malaise, chilly sensations and generalized aching. He noted no temperature elevation. The erythema attained an area of 20 by 45 mm. within 36 hours and had faded somewhat after 48 hours. This was the only systemic reaction noted in any of the subjects upon whom skin tests were performed.

Sulfadiazine has been found to be an effective therapeutic agent for both glanders and melioidosis (*M. pseudomallei*, Whitmori) in experimental animals.<sup>11</sup> Fifty per cent of infected hamsters recovered when given the full therapeutic dose of sulfadiazine for seven days. Twenty days of chemotherapy at full dosage gave 100 per cent recovery. The infection was fatal in 100 per cent of the untreated animals. These figures were the basis for

subjecting each of the last four patients in this series to a total of 20 days of chemotherapy.

### CASE REPORTS

*Case 1.* W. R. M., a 29 year old physician, was admitted to the hospital for the first time on November 27, 1944. His past history was unremarkable, except for a healed Ghon lesion, demonstrable by roentgen-ray, in the left lung field. His last positive skin reaction to old tuberculin had been in 1943.

For the six weeks preceding his illness he had been engaged in research on *M. mallei*. Approximately two weeks prior to his admission, a technician dropped a flask containing a virulent suspension of *M. mallei*. The laboratory was promptly decontaminated. The patient and one other worker (case 2) who was also in the room later developed glanders. At no time did the technician have any evidence of specific infection.

During the two weeks before admission, the patient noted generalized aches and pains, and afternoon temperature elevation to 99.3 or 99.4° F. Two days before admission, he developed a continuous sharp stabbing pain in the right middle chest, aggravated by breathing and relieved by lying on the right side.

*Course in the Hospital (First admission).* On physical examination, the patient appeared to be fatigued and moderately dehydrated. There were tender glands in the right cervical triangle. Examination of the chest revealed an area of relative dullness and slightly tubular breathing over the posterolateral aspect of the right side of the chest. No friction rubs or râles were heard. There was definite splinting of the respiratory excursions on the right. The abdomen was soft; and the liver and spleen were not felt. The remainder of the physical examination was negative.

The blood on admission showed 6,400 white blood cells per cu. mm., 60 per cent neutrophils, and 40 per cent lymphocytes. A blood culture was sterile. Three urinalyses during hospitalization were unremarkable. Subsequent blood studies showed no essential change. Two tests for cold hemagglutinins and heterophile sheep cell antibodies were negative. A roentgen-ray film of the chest on admission (figure 1A) showed an area of increased density in the right upper lobe which was roughly circumscribed, and in appearance suggested an early lung abscess. In addition, Ghon lesions were demonstrated in the periphery of both lung fields. A film taken one week later showed no change.

The patient's symptoms subsided on bed rest and supportive therapy. His temperature rose only twice to 99° F., and he was discharged on December 2, 1944 after 48 hours of normal temperature. Up to that time, there had been no serological evidence of specific infection.

*Subsequent Course.* On discharge from the hospital, the patient remained at home for one week, and again noted occasional slight afternoon temperature elevation, not over 99.4° F. During the subsequent days, he gradually resumed his work, and by December 19, 1944 was able to work a full day without temperature elevation or undue fatigue. Two chest films, on December 4 and December 11, 1944, respectively, showed no change in the appearance of the lesion in the right upper lobe. A film on December 20, however, 18 days after discharge, showed definite diminution in its size. Four complete blood counts in this interval showed persistent leukopenia and relative lymphocytosis of 40 to 50 per cent. On January 3, 1945, the patient developed symptoms typical of a common cold, with moderately productive cough and laryngitis. No temperature elevation was noted. The white blood count was 5,600 per cu. mm. with 55 per cent neutrophils and 45 per cent lymphocytes. A chest film showed further diminution of the lesion previously noted.

A skin test with 0.1 c.c. commercial mallein in a dilution of 1:10,000 was positive on January 9, 1945. Tests on normal controls were entirely negative. The serum

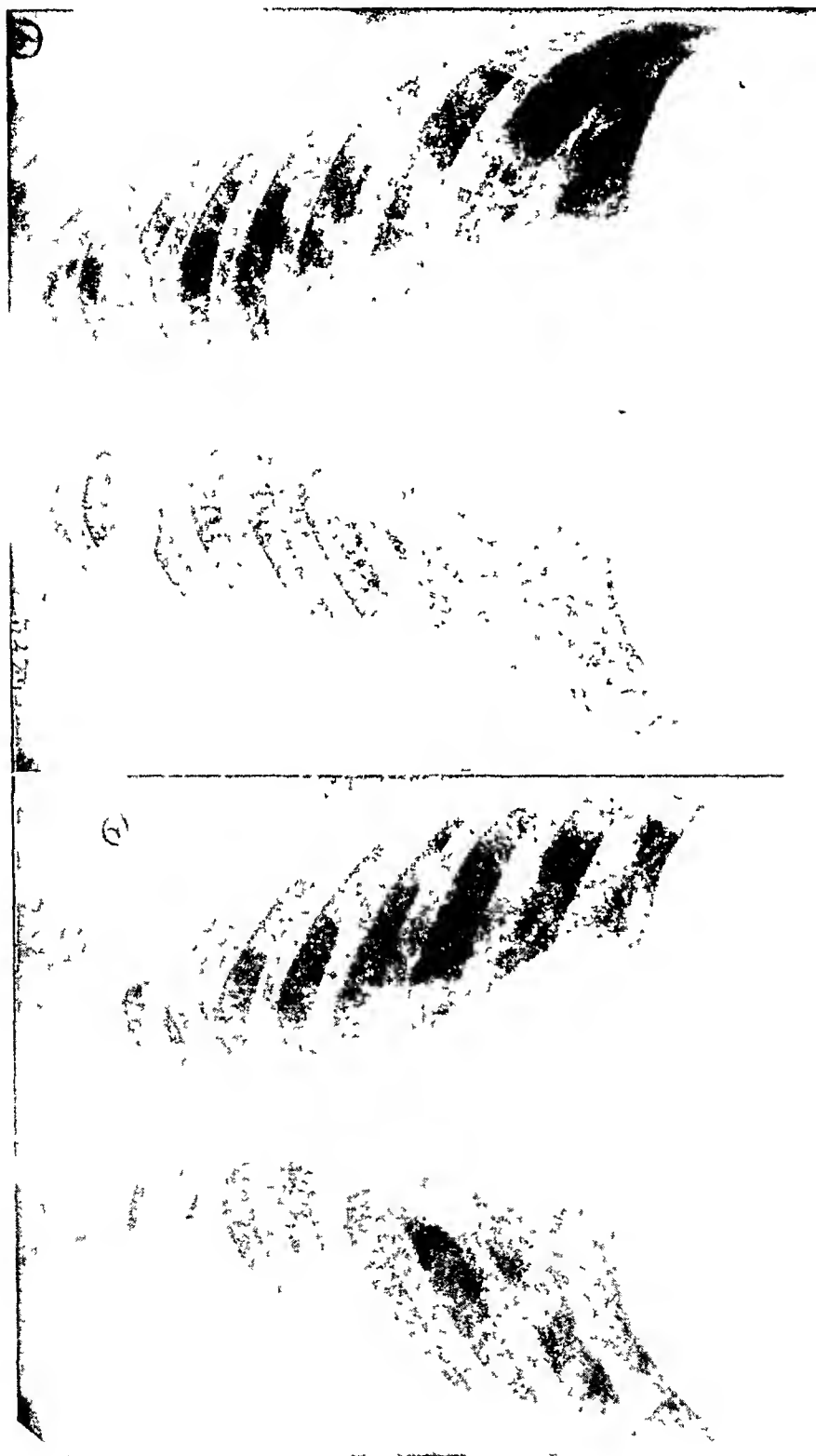
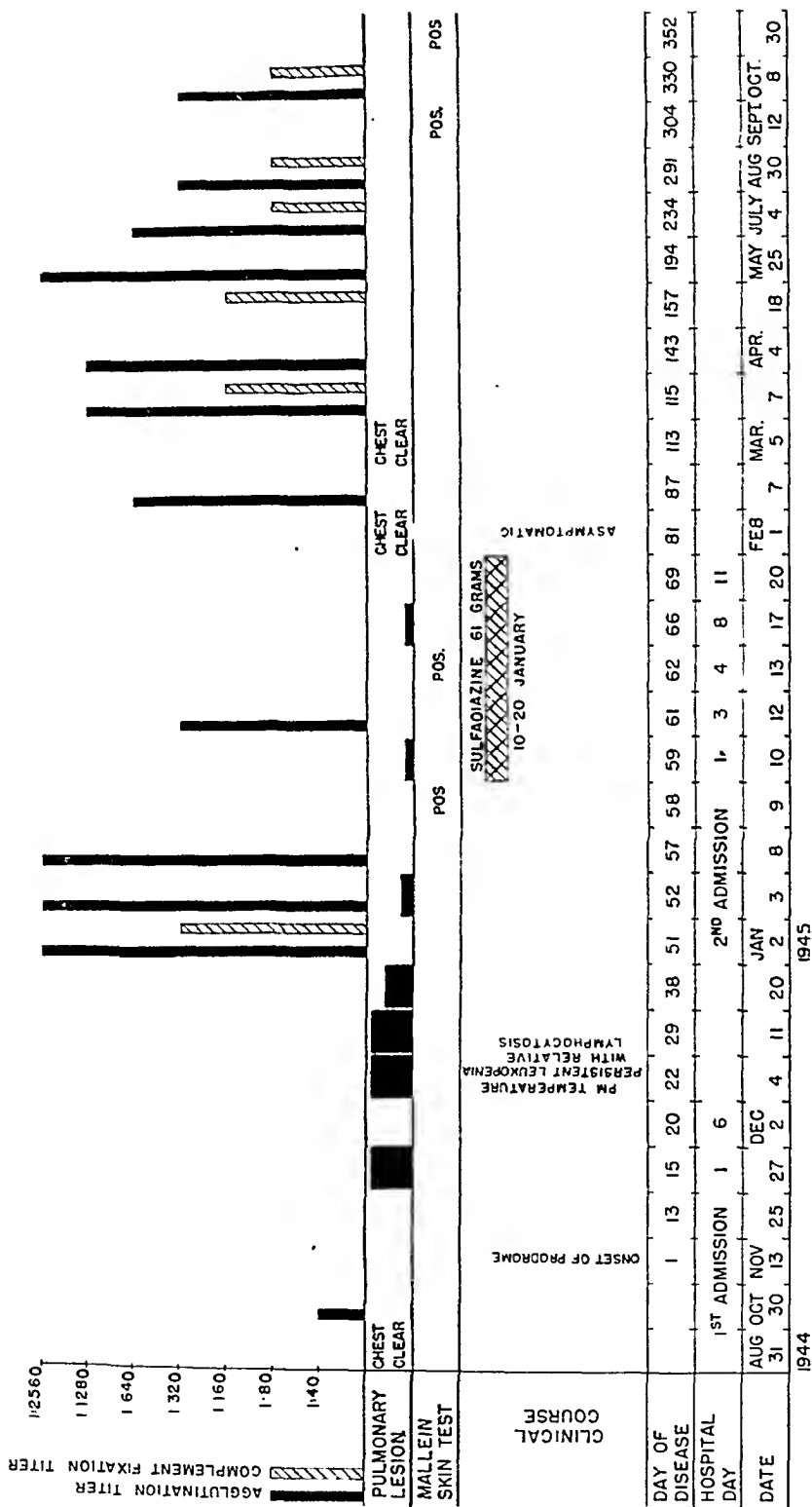


FIG. 1. A. Case 1 On admission, 14 days after onset of symptoms.  
B. Case 1. Eighty days after onset of symptoms.





titer of agglutinins for *M. mallei* had risen to 1:2560, and the complement fixation titer was 1:320. On the basis of the positive skin test and the serological evidence of infection, a diagnosis of glanders was made, and the patient was readmitted on January 10, 1945 for treatment. He had no complaints, and physical examination was entirely negative.

*Course in the Hospital* (Second admission). The patient was given sulfadiazine by mouth, 4 grams initially and 1 gram every four hours thereafter, over a 10 day period, for a total dose of 61 grams. A blood sulfadiazine level of 9 to 11 mg. per cent was maintained. The blood continued to show a slight leukopenia and relative lymphocytosis, but without abnormal elements. A blood culture taken before initiation of chemotherapy was sterile. Several attempts to find the suspected organisms in the sputum by culture on crystal violet agar failed. The serum contained no cold hemagglutinins, but the agglutinin titer for *M. mallei* remained elevated.

A chest film taken on admission showed slight residual increased density in the right upper lung field, there having been definite clearing since the last film, taken on January 3, 1945. A film taken one week later showed no change.

*Subsequent Course.* Following discharge and with one week's rest at home, the patient continued to improve, and had no further symptoms. Two subsequent chest films taken on February 1, 1945 (figure 1B) and March 5, 1945 respectively, showed complete clearing of the right lung field. The serum titer of agglutinins and complement fixing antibodies for *M. mallei* remained elevated up to 10 months after onset of illness; but within six more months had become negative. At this time, 16 months after illness, the mallein skin test was still positive.

*Case 2.* L. C., a 26 year old Doctor of Public Health, was admitted to the hospital for the first time on November 27, 1944, simultaneously with patient 1.

Since September 1944, he had been engaged in the same research program on *M. mallei*. During the 10 days prior to the onset of his illness, he had handled large amounts of suspension of this organism during the preparation of vaccines. He was present during the laboratory accident described in connection with Case 1. Two weeks prior to admission, the patient noted the onset of muscle pains, some elevation of temperature, and undue fatigue. One week before admission, his temperature rose to 100° F., and he noted progressive increase in symptoms.

*Course in the Hospital* (First admission). Complete physical examination was entirely negative. The total white blood cell count was 5,000 per cu. mm., with 70 per cent neutrophils, 26 per cent lymphocytes, and 4 per cent monocytes. Urinalysis was negative. A roentgen-ray film of the chest (figure 2A) showed a roughly circumscribed area of increased density in the periphery of the right lower lung field, similar to the lesion seen in Case 1. The appearance of this lesion likewise suggested an early lung abscess.

The patient was virtually afebrile throughout this period of hospitalization, and he noted no symptoms. Blood cultures taken at this time were sterile. Two total and differential white blood cell counts were within normal limits and a test for cold hemagglutinins was negative. The patient was discharged on the eleventh hospital day, 25 days after the onset of his illness.

*Subsequent Course.* Following discharge, the patient remained at home for four days. His temperature remained normal; but he noticed a slight nocturnal cough and small amounts of mucopurulent sputum. Four days after his discharge from the hospital, he resumed working for half days, noting elevation of temperature to 99° F. His cough persisted, and he was subject to undue fatigue. A chest film on December 18, 1944 showed a slight regression of the lesion noted on previous occasions. By December 26, 1944, the patient was working full time, and noted regular afternoon temperature elevations to 99.4 or 99.6° F, his respiratory symptoms persisting. On January 2, 1945, the patient's serum titer of agglutinins for *M. mallei* was found to be 1:2560, the only previous determination, on October 30, 1944, having been within



B

A

FIG. 2. A. Case 2. On admission, 14 days after onset of symptoms.  
B. Case 2. Sixty-seven days after onset of symptoms.

normal limits. On January 9, 1945, a skin test with 0.1 c.c. commercial mallein in a dilution of 1:10,000 was positive. On the basis of the positive skin test and the serological evidence of infection, the patient was readmitted for treatment on January 11, 1945.

*Course in the Hospital (Second admission).* The patient was given sulfadiazine, 4 grams initially, 1 gram every four hours thereafter, over a 10 day period, for a total dose of 57 grams. He remained afebrile and asymptomatic. A blood sulfadiazine level of 9 to 14 mg. per cent was maintained. The white blood cell count continued to be normal, with a normal differential. Daily urinalysis was negative. The serum titer of specific agglutinins remained elevated. A chest film taken on January 18, 1945, 67 days after the onset of his illness, showed complete clearing of the right lung field (figure 2B). The patient was discharged on January 20, and resumed normal activity.

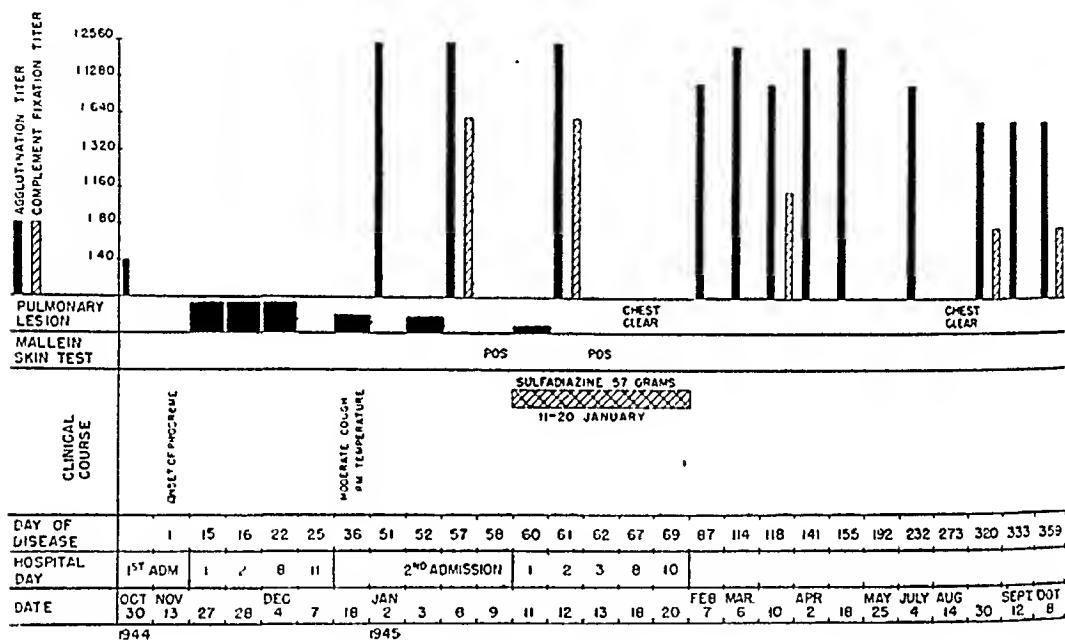


CHART 2. Case 2.

*Subsequent Course.* The patient had no recurrence of symptoms at any time. He contracted two mild upper respiratory infections during the ensuing two months. Chest roentgen-rays on each of these occasions were negative, and blood studies showed no abnormalities. The serum titer of specific agglutinins remained elevated, and skin tests repeated at long intervals remained positive, up to nine months after recovery. Sixteen months after illness, the agglutinin and complement fixation titers had become negative, but the skin test was still positive.

*Case 3.* J. F. W., a 28 year old laboratory technician, was admitted to the hospital on April 16, 1945. His past history included known infections with *Brucella abortus* and *Plasmodium falciparum*, in 1938 and 1943 respectively.

In June of 1944, the patient started to work with *M. mallei*, and was engaged in routine laboratory procedures, such as animal inoculation, plating, and serological determinations. He had no known opportunity for exposure other than that attendant upon harvesting and handling large quantities of suspension for the preparation of vaccines. His health had been excellent until his admission to the hospital on April 16, 1945, two hours after the sudden onset of dizziness, nausea, blurring of vision, backache, and chills.

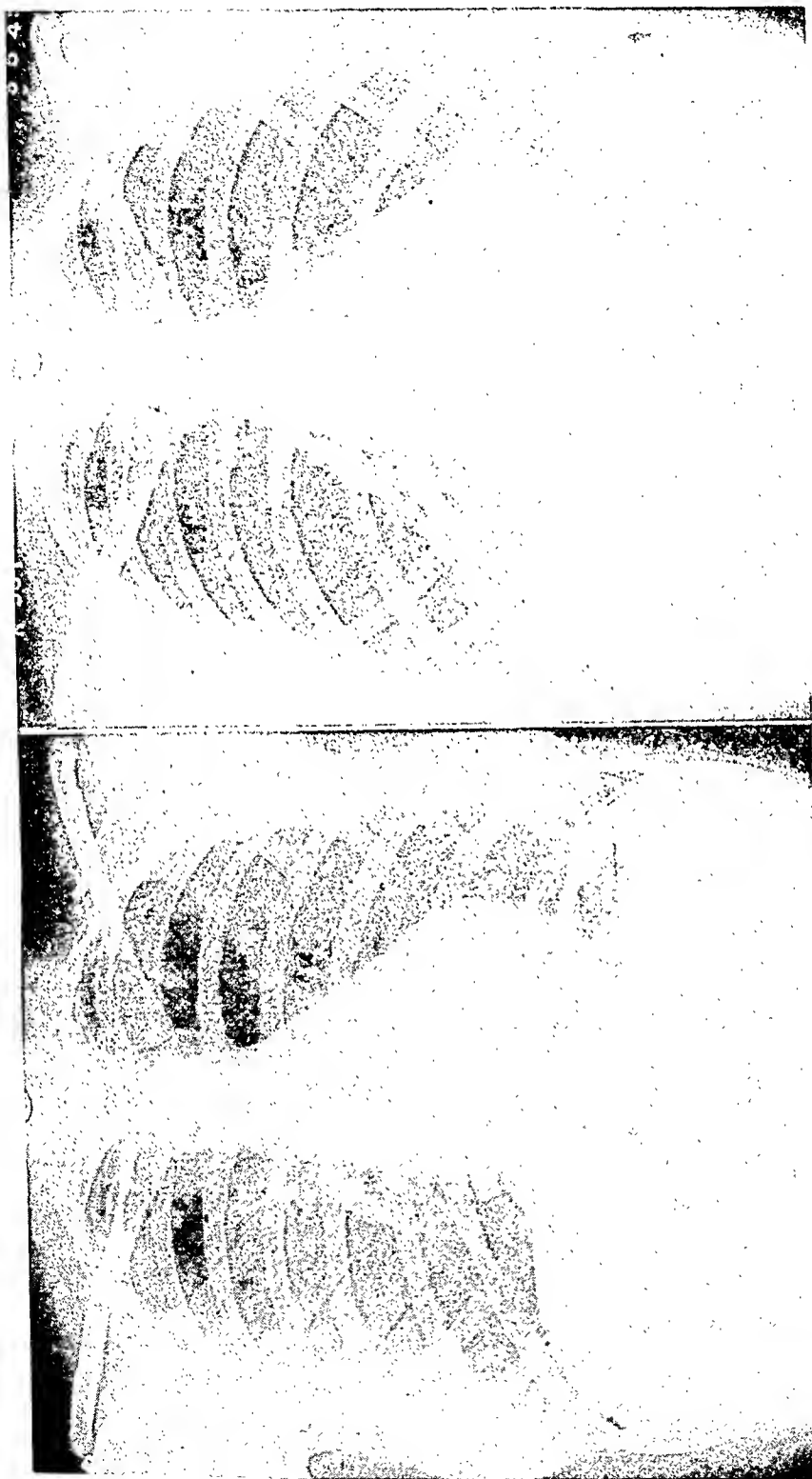


FIG. 3. A. Case 4. Fourth hospital day, five days after onset of symptoms.  
B. Case 4. Twelve days after onset of symptoms.

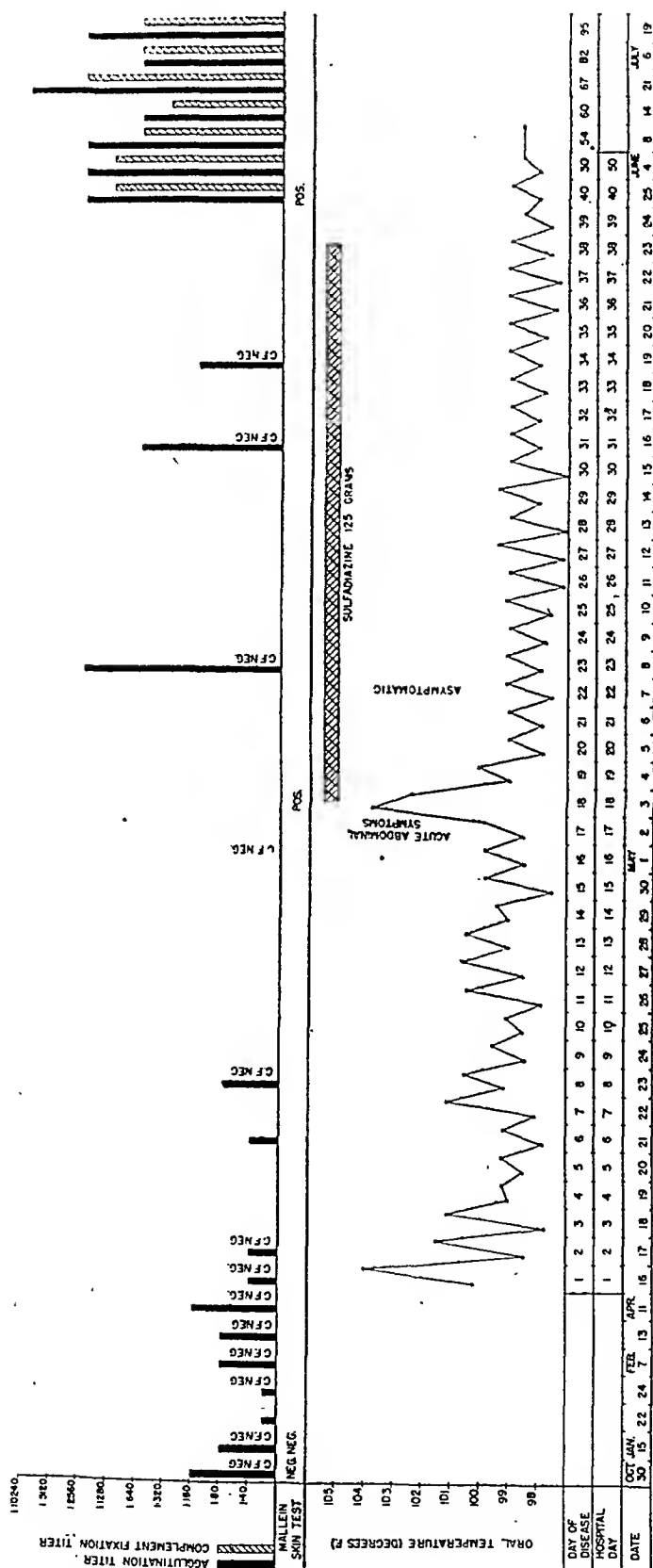
*Course in the Hospital.* Physical examination revealed a temperature of 100.4° F., a pulse of 86 per minute, and respiratory rate of 20 per minute. The patient was well oriented and coöperative. The skin showed generalized hyperkeratosis. There was no lymphadenopathy. There was marked lacrimation and photophobia. The remainder of the physical examination and a neurological examination were negative.

Two hours after admission, the patient started to complain of excruciating headache and his respirations became more rapid. Two hours later, he was found to be hyperventilating, showing marked carpopedal spasm. Neurological examination was otherwise negative. His headache failed to respond to medication or to the removal of 6 c.c. of cerebrospinal fluid, which showed normal dynamics and was negative on examination and culture. Following this short episode of tetany, the patient had a shaking chill. Blood cultures taken at this time were sterile; and thick and thin smears of the blood were negative for malarial parasites. The white blood cell count was 10,200 per cu. mm. with 84 per cent neutrophils and 16 per cent lymphocytes. Urinalysis and a portable chest roentgen-ray were negative. During the ensuing two hours, the patient's chills subsided, and his temperature rose to 103.8° F. He became nauseated and vomited three times. By midnight, his temperature had subsided to 99.8° F., after profuse diaphoresis, and by morning it was normal.

From the second to the seventeenth days, the patient's course was characterized by afternoon elevations of temperature of moderate degree, occasional headache, and continued malaise. All laboratory work, including repeated blood cultures, total and differential blood counts, stool examinations, serologic studies for enteric pathogenic organisms, for glanders, and for brucellosis, revealed nothing remarkable. Several chest films were negative.

On the twelfth hospital day, also the twelfth day of his illness, he complained for the first time of a dull aching sensation high in the left upper quadrant. Physical examination showed marked tenderness high in the left flank and under the left costal margin. The tip of the spleen was felt on deep pressure, and was extremely tender. During the next six days, he developed moderate spasm over the whole left side of the abdomen, and the tenderness increased. A flat abdominal film was negative. A skin test with 0.1 c.c. commercial mallein in a dilution of 1:10,000 on the eighteenth day became definitely, though slightly, positive in 48 hours. On the evening of the seventeenth day, the patient's temperature rose and by the following morning had reached 103.4° F. His abdominal symptoms became more acute and he obtained only slight relief from lying on the right side, with knees and hips flexed. Physical examination revealed definite spasm over the whole abdomen, most marked over the left half. There was extreme tenderness over the left upper quadrant and into the left flank, with rebound tenderness from the right side. Deep inspiration caused sharp increase in the abdominal pain. Peristalsis sounded normal in character. Blood culture and inoculation of blood into hamsters and guinea pigs failed to reveal the presence of any organism. The white blood cell count and differential were normal. A urinalysis was negative. The patient obtained relief only from morphine in repeated doses, phenobarbital sodium subcutaneously, and external heat.

On the basis of the positive skin test, a tentative diagnosis of glanders was made, and the patient was given sulfadiazine, 5 grams initially intravenously in 1,000 c.c. of normal saline, and 1 gram every four hours thereafter by mouth, for 20 days, the total dose being 125 grams. The blood sulfadiazine level was maintained at 9 to 10 mg. per cent. Within 24 hours, the patient's temperature had fallen and his symptoms and signs had subsided dramatically. During the ensuing five days, these disappeared completely, and he had only slight afternoon temperature elevation daily for the next three weeks. On the twenty-third day, the agglutinin titer for *M. mallei* had risen to 1:2560. The white blood cell count remained normal, occasionally showing a definite leukopenia with moderate to marked relative lymphocytosis. On the fortieth day, the



serum complement fixation was found to be positive in a titer of 1:1280, and a skin test was again positive, thereby confirming the diagnosis of glanders. Following the cessation of chemotherapy, the patient remained completely afebrile, and by the time of discharge, was completely asymptomatic.

*Subsequent course.* After three weeks' rest, the patient resumed full time activity, and repeated serologic studies showed continued elevation of specific agglutinin and complement fixation titers. Up to the time of this writing, he has had no recurrence of symptoms and has to all appearances completely recovered.

*Case 4.* C. H. H., a 23 year old laboratory technician, was admitted to the hospital for the first time on February 16, 1945. Her past history and family history were unremarkable. For the six weeks prior to admission, she had been engaged in routine laboratory work with *M. mallei*. On February 13, three days prior to admission, she noted the onset of moderate headache, backache and increasing fatigue; and on February 16, the day of admission, she awoke at 4:30 a.m. with marked stiffness of the neck, and photophobia. She had several shaking chills during the ensuing four hours, and her temperature rose to 102° F. She was admitted to the hospital in a semi-stuporous condition.

*Course in the Hospital* (First admission). On physical examination, the patient appeared acutely ill, and was flushed and dehydrated. She was responsive and cooperative. The neck was supple, and there was slight scleral injection. There was no lymphadenopathy. The remainder of the physical examination was entirely unremarkable. A complete neurological examination was also negative. The temperature was 101.4° F., the pulse 100, and the respirations 22 per minute.

The white blood cell count on admission was 18,000 per cu. mm., 88 per cent neutrophils and 12 per cent lymphocytes. The urine examination was negative. A spinal puncture performed shortly after admission revealed clear cerebrospinal fluid with normal dynamics. The sugar was 65 mg. per cent; there were seven lymphocytes and the globulin was not elevated. The fluid was sterile on culture. The removal of 6 c.c. did not relieve the severe headache from which the patient was suffering. A chest roentgen-ray taken on admission showed a small, roughly spherical area of increased density in the right upper lung field, at the hilum, measuring approximately 3.5 cm. in diameter. Throat cultures and blood cultures revealed nothing significant.

Because of the rising temperature, the leukocytosis, and the patient's acutely ill condition, she was given sulfadiazine, 5 grams initially intravenously in 1,000 c.c. of normal saline, and 1 gram by mouth every four hours thereafter, for a total dose of 34 grams. She also received penicillin, 60,000 units every three hours for four doses, and 30,000 units every three hours thereafter, for a total dose of 1,050,000 units over the first four hospital days.

The patient's temperature is charted in chart 4. Definite physical signs remained absent, and she continued to be in a semi-stuporous condition, though remaining responsive and cooperative. On the second day, the blood showed a total white cell count of 8,000 per cu. mm., 77 per cent neutrophils, 23 per cent lymphocytes. The serum titers of agglutinins for *M. mallei* was 1:160, and complement fixation was negative. During this time, she complained of severe, intermittent headache, photophobia, and malaise. Physical examination remained unremarkable except for moderately enlarged and slightly tender lymph nodes in the right anterior and posterior cervical triangles, which had not been felt on admission. A lumbar puncture, performed on the fourth hospital day, showed clear cerebrospinal fluid with normal dynamics, normal sugar, protein, and cellular content. The fluid was sterile on culture and on mouse inoculation. A chest film on the fourth day (figure 3A) showed no change from the film taken on admission. The agglutinin titer on this date was 1:640; and complement fixation remained negative. A blood count showed 5,200 white

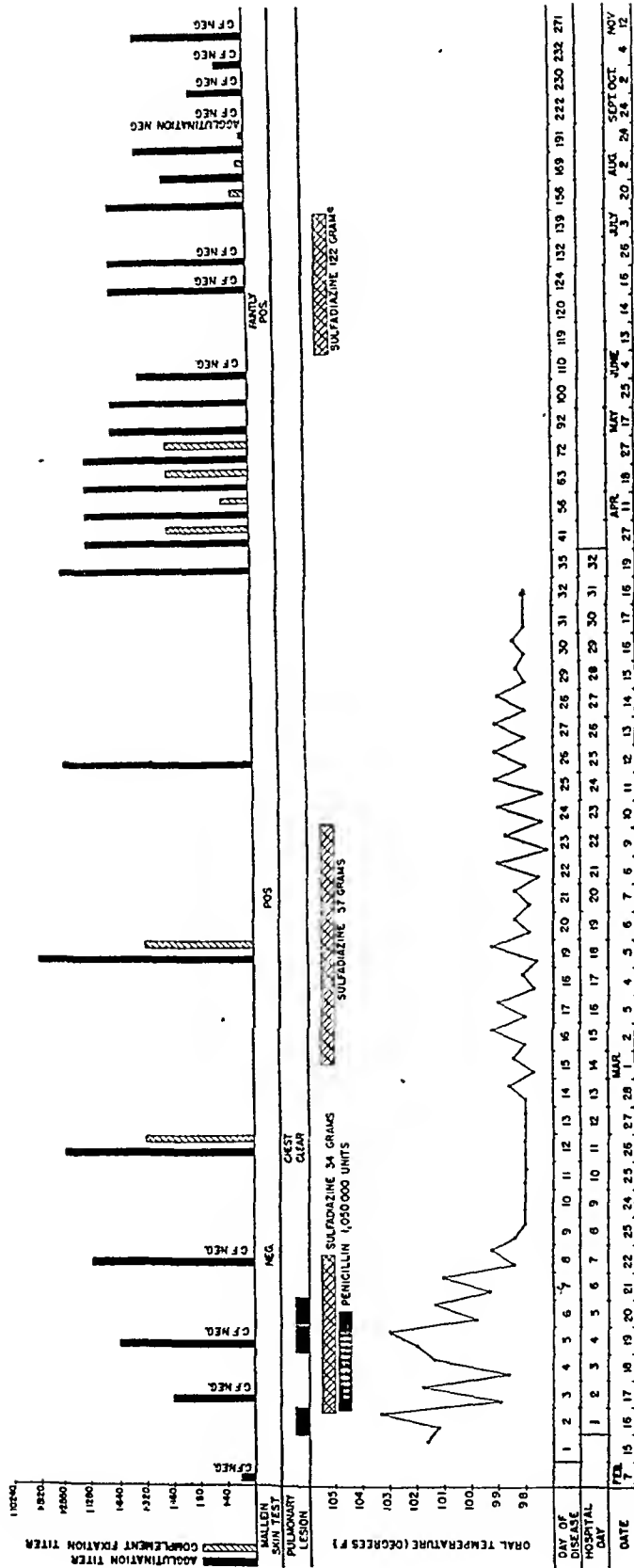


CHART 4. Case 4.



blood cells per cu. mm., 75 per cent neutrophils, 25 per cent lymphocytes. During the ensuing 48 hours, the patient's temperature subsided gradually, and by the seventh day was normal. Sulfadiazine administration was stopped on the seventh hospital day because of a falling white blood cell count and the appearance of red and white blood cells in the urine. A skin test on the seventh day with 0.1 c.c. commercial mallein in a dilution of 1:10,000 showed no reaction in 24 or 48 hours. The agglutinin titer had risen to 1:1280, complement fixation remaining negative. Tests for heterophile sheep cell agglutinins and for cold hemagglutinins were negative.

The patient continued to be afebrile and asymptomatic except for occasional headache which was relieved by codeine sulfate. By the eleventh hospital day, her titer of agglutinins had risen to 1:2560, thereby supporting the diagnosis of glanders, and suggesting a plausible explanation for the pulmonary lesion seen on roentgen-ray examination. Chest films taken on the twelfth (figure 3B) and eighteenth days, respectively, showed complete clearing of the right lung field.

After a test dose of 2 grams of sulfadiazine, to which the patient showed no untoward reaction, administration of the drug was resumed on the fourteenth hospital day, 4 grams initially, and 1 gram every four hours thereafter through the twenty-third hospital day. This represented an additional dose of 57 grams, with the previous period of chemotherapy totalling 91 grams. A blood sulfadiazine level of 9 to 10 mg. per cent was maintained during both periods of therapy. On the twentieth hospital day, the twenty-first day of illness, the skin test was positive; the agglutinin titer had reached 1:5120; and the complement fixation titer was 1:320. The patient was discharged on March 19th, 33 days after the onset of her illness.

*Subsequent Course.* The patient continued to experience moderate fatigue, and noted occasional afternoon temperature elevations. The mallein skin test remained positive; but by June 4, 1945, 10 weeks after discharge from the first hospitalization, the serum titer of agglutinins for *M. mallei* had dropped to 1:320 and complement fixation was negative. Because of persistent, vague symptoms, and the decline in serological response, the patient was readmitted to the hospital on June 9, 1945 for reevaluation.

*Course in the Hospital* (Second admission). Physical examination on this admission was negative, except for a temperature of 99.4° F. The white blood cell count was 12,000 per cu. mm., 72 per cent neutrophils, and 28 per cent lymphocytes. The agglutinin titer on June 18 was 1:640, and complement fixation was negative. A chest film revealed nothing abnormal, and inoculation of throat washings and urine into hamsters gave negative results. A mallein skin test was faintly positive. Because of the possibility of continued activity of disease, the patient was started on another course of sulfadiazine, receiving 4 grams initially, and 1 gram every four hours thereafter for a total dose of 122 grams. She had two or three moderately severe asthmatic spells, the etiology of which was obscure. Chest roentgen-ray examinations were consistently negative. Films of the paranasal sinuses and the teeth failed to reveal any abnormalities. She was discharged from this second admission on August 24, 1945, after one week of normal temperature.

*Subsequent Course.* At this time, the patient was given 30 days of convalescent leave, during which she noted occasional afternoon elevations of temperature, but continued to improve steadily. By the end of October, 1945, approximately eight months after the onset of her primary illness, she was completely asymptomatic and showed no sign of active disease.

*Case 5.* C. J. N., a 28 year old veterinarian, had been handling *M. mallei* for approximately one month prior to his admission to the hospital on September 4, 1945. There had been several occasions during the course of his work on which small amounts of infectious aerosol had been inadvertently produced and probably inhaled. On August 20, 1945, 15 days prior to admission, he noted the onset of severe headache.

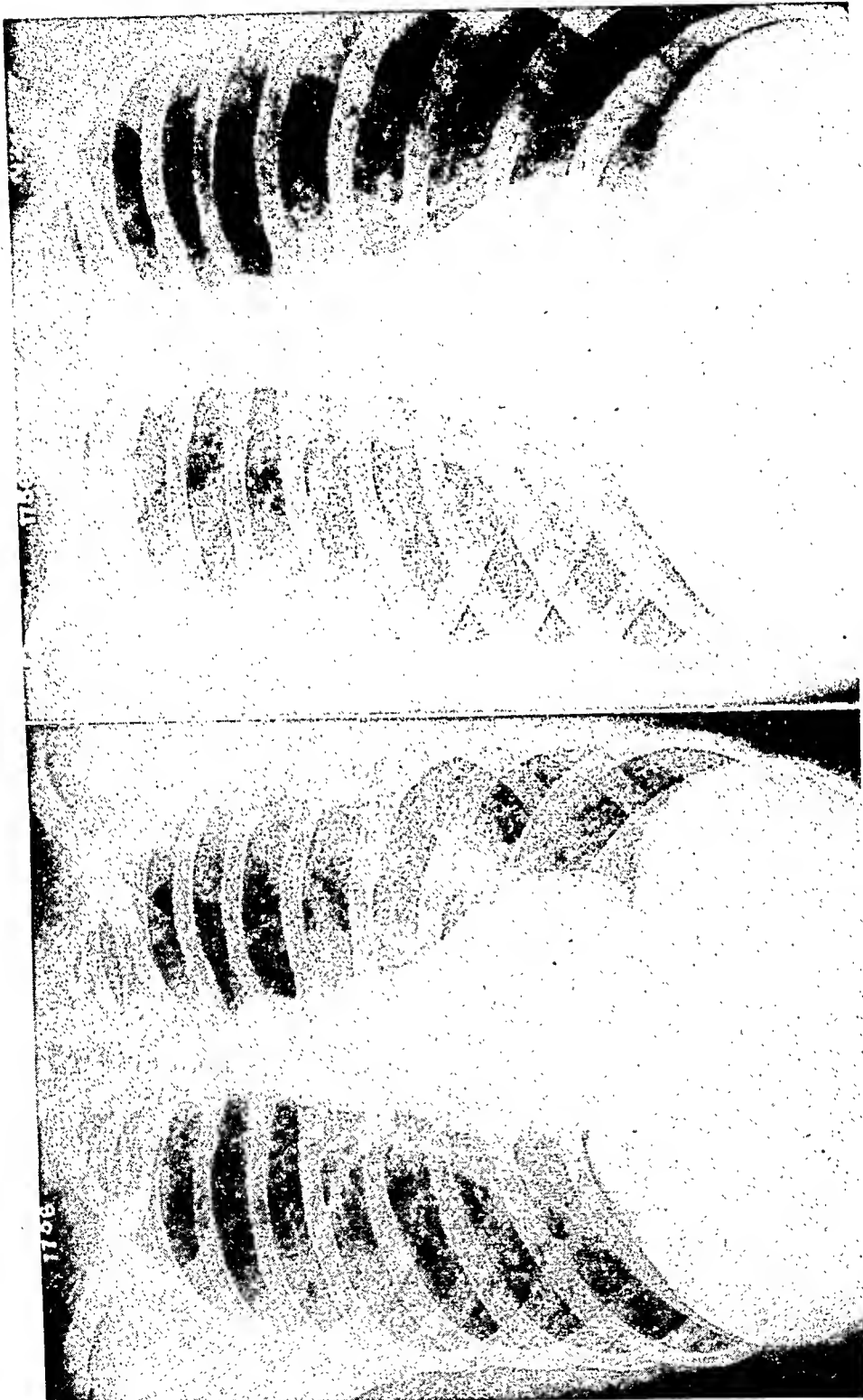


FIG. 4. A. Case 5. On admission, 16 days after onset of symptoms.  
B. Case 5. Sixty-four days after onset of symptoms.

In the ensuing three to four days he also developed severe backache, and by August 27, one week before admission, he had extreme malaise and undue fatigue which persisted for an additional three to four days. On the evening of August 28, six days before admission, his temperature was 102.8° F. At this time he also noted tenderness and swelling of the cervical lymph glands. By August 29, five days prior to admission, he had improved somewhat, but noticed for the first time an aching pain in the left side of his chest, aggravated by deep inspiration. He continued to feel fatigued and the pain in the chest persisted. He did not complain of cough at any time.

*Course in the Hospital.* The temperature was normal. The posterior pharyngeal wall was injected, but there was no exudate. Small tender lymph nodes were palpable in the anterior and posterior cervical chains. Glands were also palpable in the

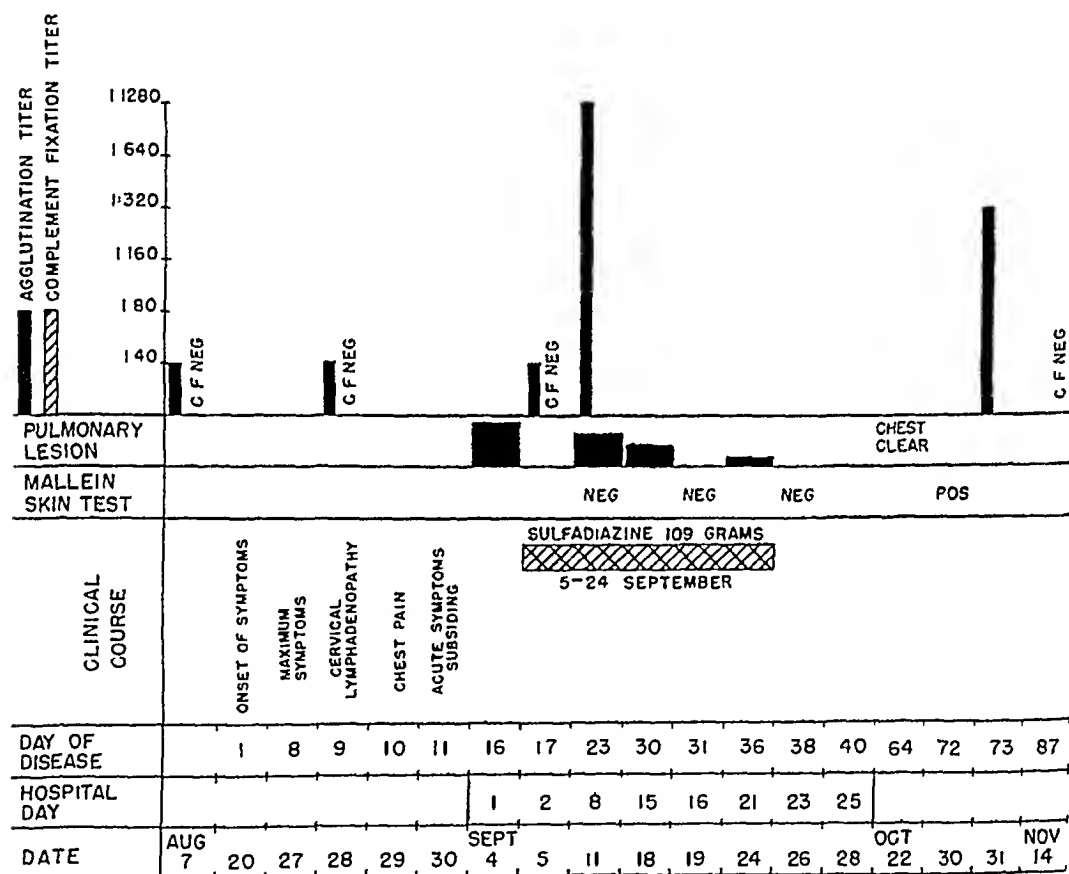
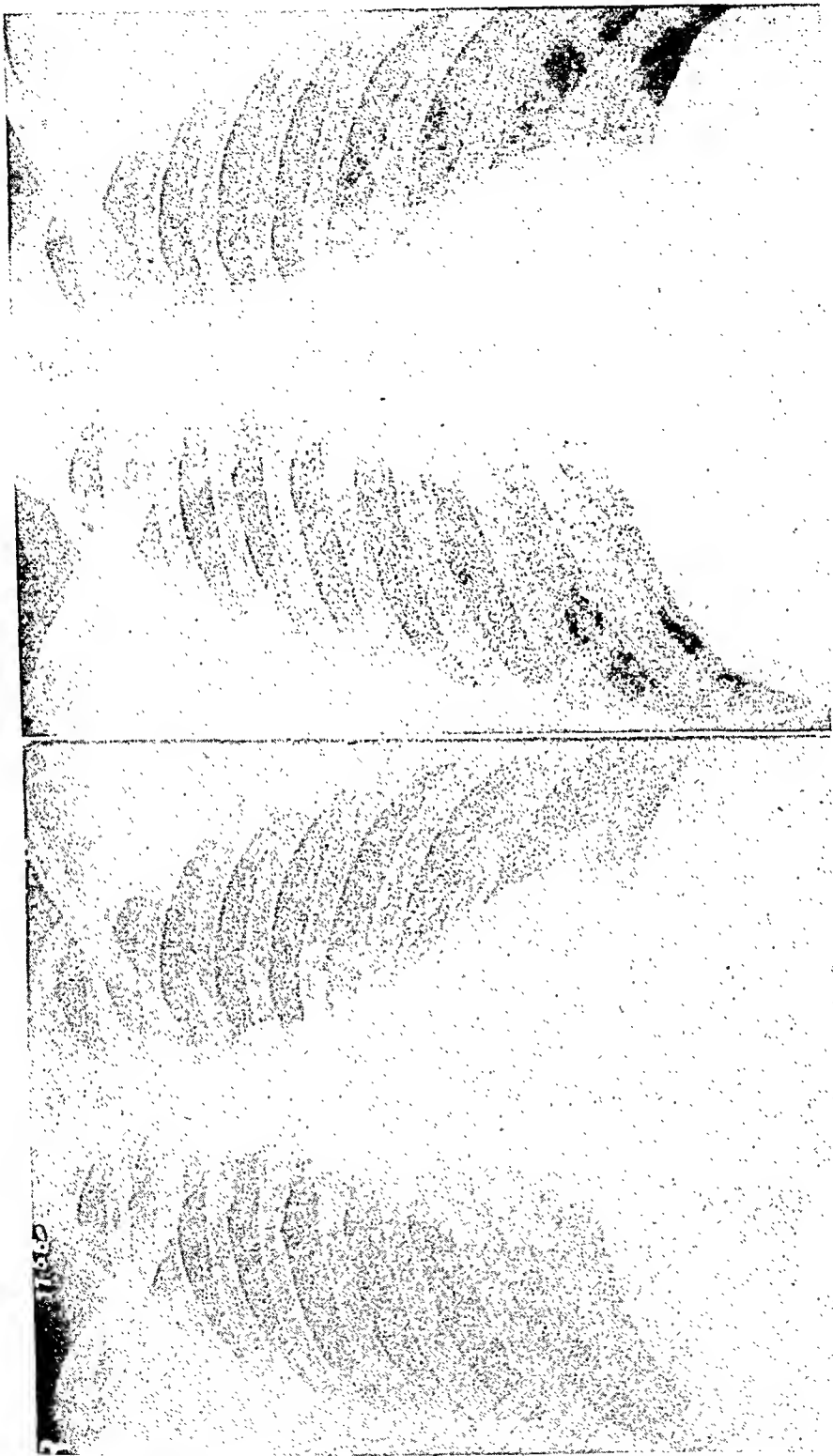


CHART 5. Case 5.

axillary, epitrochlear, and inguinal regions, but were not tender. Physical examination was otherwise unremarkable. The white blood cell count was 7,800, 60 per cent neutrophils, 40 per cent lymphocytes. Eleven subsequent total and differential blood counts, taken on every second day, were normal except for occasional slight relative lymphocytosis. The agglutinin and complement fixation titers for *M. mallei* are given in chart 5. Cough plates taken on crystal violet agar on admission gave no growth. Tests for cold hemagglutinins and heterophile sheep cell antibodies were negative.

A chest film taken on admission (figure 4A) showed an area of increased density in the mid left lung field, extending to the periphery and involving almost the entire middle third of the left lung field. Films taken on the eighth hospital day, the twenty-



A  
B  
FIG. 5. A. Case 6. On admission, eight days after onset of symptoms.  
B. Case 6. Twenty-two days after onset of symptoms.

third day of disease, showed slight reduction in the size of this lesion. There was further reduction in the extent of the lesion during the ensuing six days.

Because of the probability of exposure to and infection with *M. mallei*, the patient was started on sulfadiazine, 4 grams initially by mouth, and 1 gram every four hours thereafter, over 20 days, for a total dose of 109 grams. A blood sulfadiazine level of 10 to 12 mg. per cent was maintained. During the last 10 days of therapy, the patient showed regular afternoon temperature elevations to 99 or 99.2° F. The skin test with 0.1 c.c. of commercial mallein in a dilution of 1:10,000 did not become positive until October 30, 1945, 72 days after the onset of his illness, one month after discharge from the hospital. The first clear chest film was obtained on October 22, two months after onset of disease, by which time the agglutinin titer had shown a significant rise. The complement fixation titer remained negative throughout. Up to the time of this writing, six months after admission to the hospital, this patient's recovery is apparently complete.

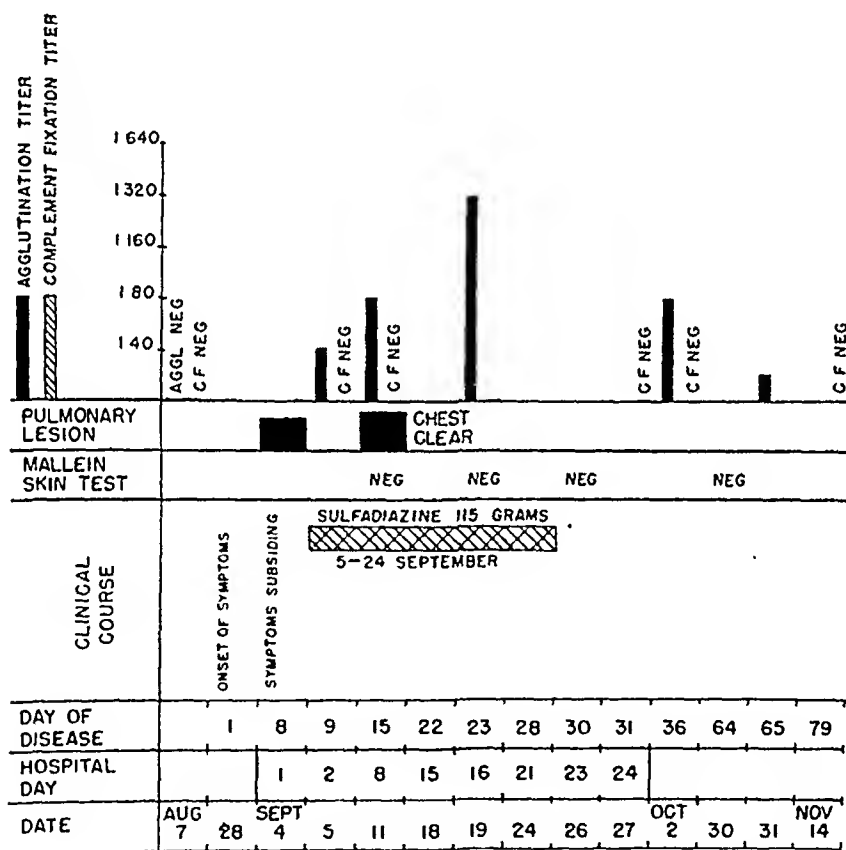


CHART 6. Case 6.

Case 6. L. C. F., a 33 year old veterinarian, was admitted to the hospital on September 4, 1945. His past history revealed an attack of undulant fever in 1937, without subsequent relapse.

For the month prior to admission, the patient had been engaged in the same laboratory work as case 5, involving routine culture transfers, inoculations and harvesting of *M. mallei*. He likewise had occasional opportunities for infection in the process of certain laboratory manipulations which may have resulted in the inhalation of organisms. On August 10, 1945, approximately three weeks before admission, he had

received for study a new and more virulent strain of *M. mallei*. On August 21, 10 days later, mass culture of this strain was initiated in the laboratory. The patient knew of no gross laboratory accidents during the two weeks which followed, prior to his hospitalization. He was in good health until about August 28, one week prior to admission, when he noticed that his throat was sore. On the following day, he experienced increasing malaise and noted pain in the left side of his chest, aggravated by deep inspiration. He developed persistent headache, and for two or three days had moderate diarrhea, without other gastrointestinal symptoms. On August 30, five days before admission, he felt feverish, but his temperature was not taken.

*Course in the Hospital.* During the few days immediately preceding his admission, his symptoms had started to subside, and physical examination was entirely negative. The white blood cell count on admission was 7,600, 68 per cent neutrophils, 32 per cent lymphocytes. The agglutinin titers for *M. mallei* are shown in chart 6. The complement fixation titer remained negative throughout the period of observation. Tests for cold hemagglutinins, heterophile sheep cell agglutinins, and *Brucella* agglutinins were negative.

A chest film taken on admission (figure 5A) showed an area of increased density in the left lower lung field lateral to the pericardial outline, irregular in shape, suggesting, unlike the lesions in the other cases, a pneumonitis. Films on the eighth hospital day, the fifteenth day of disease, showed slight extension of this same area, which, however, by the twenty-second day of disease had disappeared completely (figure 5B).

The patient was afebrile throughout his hospitalization. Because of the close similarity of this case to Case 5, both from epidemiological and clinical points of view, and by reason of his probable exposure to *M. mallei*, he was given sulfadiazine, 4 grams initially, and 1 gram every four hours thereafter. The total dose, over a 20 day period, was 115 grams, and a blood sulfadiazine level of 10 to 11 mg. per cent was maintained. Skin tests with commercial mallein in a dilution of 1:10,000 were consistently negative. The patient was ambulatory during the latter part of his hospitalization and was discharged on September 28, 1945.

*Subsequent Course.* Following discharge, he continued to improve subjectively. The skin test never became positive. The agglutinin titer, by two months after the onset of illness, had fallen to 1:20, complement fixation remaining negative. Up to seven months after illness, this patient has had no further sign of disease.

## EPIDEMIOLOGY

During the period covered by the research program, a total of 22 persons worked in a single, isolated, relatively small laboratory building at various times. Thirteen of these were actually engaged in laboratory work. The other nine were employed in general maintenance. The six patients in this report represent 27 per cent of the total number of people who may have at one time or another been exposed to infection, and 46 per cent of the persons actually working in the laboratories.

The incubation period cannot be accurately determined in any of these cases. In retrospect, however, the patients were able to recall what appeared to have been relatively insignificant incidents during the course of their laboratory work, which may have been the source of their infections. The first two patients were both involved in the same laboratory accident, as has already been pointed out, two weeks prior to the onset of their symptoms.

Ten to 14 days before the onset of their symptoms, patients 1, 2, 3, and 4 had each been engaged in washing the growth of organisms from agar plates during the preparation of vaccines. Although protective clothing was worn and extreme care was exercised, the inhalation of an aerosol may well have occurred. Patient 4 may have been the victim of a technical oversight. After washing growth off of agar surfaces for the preparation of suspensions, she had failed to kill the organisms by heat prior to making up dilutions for standard turbidity measurements. This mishap occurred two weeks before the onset of her symptoms. About two weeks prior to their admission, patients 5 and 6 had been engaged in procedures involving the aeration of cultures by bubbling air or oxygen through liquid medium. They recalled that on one or two occasions the containers had been opened immediately after the air current had been turned off, rather than after a period of delay long enough to minimize the escape into the room of the infectious aerosol in the upper part of the container. It will be recalled that these two patients had been working with a strain of *M. mallei* of greater virulence than that to which the first four patients had been exposed.

If the incidents enumerated above were the occasion for actual exposure in each case, the incubation period would then appear to have been 10 to 14 days for all six patients.

The mode of infection cannot be proved in any case. The usual precautions were taken during all laboratory procedures. Regular check-up studies consisting of culture of air samples and of swabs of tables, benches, refrigerators, incubators, and other equipment, failed to reveal any persistent contamination. Triethylene glycol aerosols were put up in the laboratory rooms during procedures which were thought to be particularly hazardous. All personnel working with the organisms wore special laboratory clothing and were fitted with operating gowns and surgical gloves when handling infectious material, thus minimizing the possibility of infection by other than the respiratory route. The incidents recalled by each patient as enumerated above suggest that there had been opportunity for the creation and inhalation of an infectious aerosol in each instance. These opportunities, furthermore, were supplemented by the fact that all six patients had at one time or another been in the habit of using mouth suction on plugged dilution pipettes and of blowing out the last drop from pipettes calibrated to the tip. The preponderance of pulmonary lesions (five out of six cases) and the various opportunities for respiratory exposure suggest that the respiratory tract was the main route of infection.

#### DIAGNOSIS

*Laboratory Findings.* *M. mallei* was not isolated from any of these patients. Blood cultures were taken in all cases on one or more occasions, with both routine medium and special medium designed to enhance the growth of *M. mallei*. Further attempts to isolate the organism by inocula-

tion of blood into hamsters met with no success. Throat washings and sputum, after incubation with penicillin, were cultured on crystal violet agar without positive results.

The diagnosis of glanders was substantiated by a significant and sustained rise in the serum titer of agglutinins for *M. mallei* in five cases, and by a less marked rise in titer in the sixth case. In cases 1, 2, 3, and 4, the complement fixation test also became positive. In the absence of positive complement fixation in the sixth case, the rise in agglutinin titer to 1:320, even though this did not exceed the level encountered in normal sera, was significant, since repeated tests on normal controls had shown no such wide fluctuation.

The only other striking laboratory finding was a persistent leukopenia and relative lymphocytosis. With recovery, the lymphocytosis tended to subside, and the differential count gradually resumed normal proportions.

*Skin Test with Mallein.* The significant serological response in the first five cases was accompanied by a positive reaction to the intracutaneous injection of 0.1 c.c. of commercial mallein in a dilution of 1:10,000. On each occasion; where skin tests were performed on patients in this series, the same test with the same material was performed on individuals who were known to be free of infection. The first and second patients (who had long since recovered) were used as positive controls in testing the last four patients. No false positive results were encountered among the usual negative controls and all of the known positives reacted consistently.

*Roentgen-Ray Findings.* The roentgen-ray findings in Cases 1, 2, 4 and 5 were similar, in that the lesions suggested lung abscess in the early stages, before cavitation and necrosis, being fairly well circumscribed and roughly circular in outline. The lesion in Case 6, however, had more the appearance of pneumonitis, being more diffuse and infiltrating in character. Robins<sup>3</sup> states that the pathological findings in human infections with *M. mallei* constitute anything from a moderate bronchial pneumonia to a focal necrotizing lesion more nearly approximating lung abscess. It is thus apparent that the roentgen-ray findings in Case 6 are not inconsistent with the diagnosis of glanders. There was no evidence by roentgen-ray of pleuritis or pleural effusion. Patients 1, 5, and 6, however, complained of pain which suggested pleural irritation.

## TREATMENT

All of the patients in this series were treated with sulfadiazine because of its demonstrated efficacy in experimental glanders and melioidosis in animals. Patients 1 and 2 were treated some time after the discovery of their pulmonary lesions, the correct diagnosis being established during their convalescence. Sulfadiazine was given to these two patients with the object of preventing possible spread or exacerbation of disease. There was obviously no opportunity to observe any clinical response to chemotherapy.

In the last four cases, sulfadiazine was given for a total of 20 days because of the indications from the experimental work that this amount of



therapy was essential for 100 per cent recovery in animals. Furthermore, the administration of the drug in these four cases was started nearer or during the acute stage of disease, when the diagnosis of glanders appeared probable. In Case 3, the diagnosis was complicated by a past history of brucellosis and malaria. The acute abdominal signs and symptoms were interpreted as evidence of splenitis or perisplenitis. These manifestations were of interest because of the extensive splenic granulomatous lesions which occur consistently in animals infected with *M. mallei*.<sup>12, 13</sup> The most definite response to treatment was observed in Case 3, who showed a marked drop in temperature and definite symptomatic improvement within 48 hours after the institution of chemotherapy. This clinical response appeared to be significant.

Case 4 also showed a fairly clear-cut clinical response to therapy, though her improvement was not so dramatic as that of Case 3. A second course of sulfadiazine was given in this case because of the recurrence of fever and constitutional symptoms.

In Cases 5 and 6, whose respective courses were almost exactly parallel, chemotherapy was initiated shortly after the acute stage of disease had passed because of the suggestive epidemiologic evidence and the definite pulmonary lesions. Since these two patients appeared to be improving before they received sulfadiazine, it is difficult to assess the therapeutic action of the drug and its effect on the course of disease. It was thus impossible to determine how long treatment should have been continued for maximum benefit. It is of interest that the pulmonary lesions in Cases 5 and 6 showed complete regression at the end of eight and three weeks, respectively, whereas the lesions in Cases 1 and 2 were still visible after more than eight weeks. It will be recalled that Cases 1 and 2 received 10 days of chemotherapy not during the acute stage, but long afterwards, and while the pulmonary lesions though still demonstrable, were regressing. Cases 5 and 6, however, received twice as much treatment, and that chronologically much sooner after the onset of acute illness, while pulmonary lesions were ostensibly at their height.

#### SUMMARY AND CONCLUSIONS

1. Six cases of human glanders are presented in detail.
2. The diagnosis, suspected on the basis of epidemiologic evidence and clinical findings, was substantiated by the results of serum agglutination and complement fixation tests, and response to mallein skin tests in five cases. In the sixth case, the serological data were not clear cut, and the skin test was consistently negative. Because of striking similarity to Case 5, from both clinical and epidemiologic viewpoints, he was considered to be a case of glanders, and was therefore included in this series.
3. All six patients were treated with sulfadiazine because of striking evidence of its efficacy in animals infected experimentally with *M. mallei*. From a study of these cases there are indications that human infection with

*M. mallei* is amenable to treatment with sulfadiazine, though no definite conclusions can be drawn from so small a series. It is clear, however, that sulfadiazine warrants further adequate trial in human glanders.

The authors are indebted to Major H. V. Ellingson, M.C., U.S.A., Post Surgeon, Captain E. S. Miller, M.C., A.U.S., and Captain H. L. Bookwalter, M. C., A.U.S. for assistance in the care and management of these patients. They wish also to express their appreciation to Lieutenant Colonel A. O. Hampton, M.C., A.U.S., Walter Reed General Hospital, for reviewing the roentgen-ray films, and to Captain R. A. West, Sn.C., A.U.S., 1st Lieutenant F. M. Schabel, Sn.C., A.U.S., and Ensign L. Cravitz, H(S), U.S.N.R. for much of the laboratory work.

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# CASE REPORTS

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## CUTANEOUS DIPHTHERIA WITH TOXIC MYOCARDITIS: REPORT OF FATAL CASE WITH NECROPSY FINDINGS \*

By SAUL SOLOMON, Lieut. Col., M.C., A.U.S., F.A.C.P., and CARL W. IRWIN, Capt., M.C., A.U.S.

IN the surgery of war wounds, one must expect to lose a number of patients whose injuries are extensive. However, when the injury is in itself trivial and a fatal complication results, the outcome is apt to disturb the equanimity of those who have attended the case and to point the moral that there are no trivial war wounds. Every case is potentially serious and the results unpredictable.

The case we wish to report is that of a soldier who developed abrasions of the buttocks from riding a mule. These abrasions became infected with Klebs-Loeffler bacilli, and he died of toxic myocarditis.

Cutaneous diphtheria as well as wound infection by the Klebs-Loeffler bacillus was apparently uncommon on the Western front. The First General Medical Laboratory which received a fair sampling of bacteriologic material from U. S. Army Hospitals in the United Kingdom found only a few cases of cutaneous diphtheria.<sup>1</sup> Reports from the Middle East, however, indicate that the condition was much more frequent there. Cameron and Muir<sup>2</sup> reported a series of 66 cases of cutaneous diphtheria from Northern Palestine. The lesions occurred on unbroken skin as well as on scratches, insect bites, impetigo or other skin lesions. A large percentage of the patients had diphtheria of the nose and throat, and it appears that the cutaneous infection was due to autoinoculation. Twelve of the cases developed paralysis of spinal or cranial nerves usually as a late development. Hunt's<sup>3</sup> experiences in North Africa were very similar. He saw 76 cases of which 19 developed polyneuritis. Two patients developed diphtheritic myocarditis and died. Benstead<sup>4</sup> reported 31 cases of cutaneous diphtheria from India, three of which developed peripheral neuritis. Melchior<sup>5</sup> observed a few cases occurring on various ulcers, burns, and amputation stumps. Myers<sup>6</sup> pointed out that death may occur from respiratory paralysis, Adams-Stokes attacks or myocardial decompensation, and emphasized that once these degenerative sequelae of diphtheria have appeared, treatment with antitoxin has little if any effect on the outcome.

The characteristic chronic diphtheria ulcer is oval with a raised rolled edge and a deep unhealthy base usually covered by a dirty gray membrane. The lesion in our case was quite different, resembling more a superficial weeping and crusting dermatitis. The common chronic sores of diphtheria are particularly indolent and may take months to heal despite therapy. Although this may be time-consuming, it is not the chief reason for the necessity of early bacteriologic diagnosis. The matter is urgent because of the complications that the diphtheria toxin may cause, which are the same whether the infection is in the upper respira-

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tory tract or on the skin. The commonest is peripheral neuritis involving as a rule only the motor nerves. The paralysis nearly always disappears completely in weeks or months. However, the most serious complication and the cause of the majority of deaths in Klebs-Loeffler bacillus infections is toxic myocarditis, which was the cause of death in our case.

The treatment has not changed despite the advent of chemo-therapy. Diphtheria antitoxin must be employed. The dosage is 20,000 to 60,000 units according to Myers,<sup>6</sup> but it is our impression that the higher dose is preferable. One should not wait before commencing treatment, because once the toxin has been fixed in the peripheral nerves or myocardium, the damage cannot be undone. As a British writer<sup>7</sup> points out, the medical officer should act on clinical judgment and morphologic appearance of bacteria in smears in deciding whether to give antitoxin. Otherwise by delaying specific treatment until laboratory identification is complete he may himself perpetrate a virulence test on a human subject with irreversible effects. Our case did not receive treatment, since the diagnosis was not made until after his death. Even if he had received antitoxin when first seen by us, it would have been too late, since toxic myocarditis was already far advanced.

The source of the virulent Klebs-Loeffler bacilli may be the patient's own upper respiratory tract or that of another patient, the physician, nurse, or attendant. Throat cultures should be taken of the patient and all his contacts. Our patient had the condition before his admission to our hospital, and it is likely that he was infected by a carrier when his lesion was dressed. This would be strong argument in favor of keeping wounds covered except when dressings are changed and insisting on masks being worn by attending personnel at such times.

#### CASE REPORT

A 25 year old white soldier who was wounded in action on Aug. 8, 1944 by shell fragments, sustained lacerations of the right thigh, right leg, and right thumb. He was treated in an Aid Station where the wounds were debrided, and he was given sulfathiazole, a total of 6 gm. in 24 hours. He also complained at that time of abrasions of both buttocks, incurred from riding a mule. The abrasions were cleaned and appeared insignificant. On Aug. 9, he was transferred to a Clearing Station where it was found that he had a fever of 101.6° F. A diagnosis was made of inguinal lymphadenitis secondary to infection of the lacerations of the thigh. Hot compresses were applied to the right thigh, and the patient received sulfadiazine from Aug. 9 to Aug. 15. On Aug. 16 a diagnosis was made of perineal epidermophytosis, referring to the infected abrasions of the buttocks, and potassium permanganate compresses were applied. The patient was transferred through several more installations before reaching this hospital on Aug. 20 at 2:30 p.m. as a litter case.

Physical examination on admission showed healing wounds of the right thigh, right leg and right thumb. On the lower medial surfaces of both buttocks there were superficial crusted lesions, each approximately two inches square, covered with a slight tan-colored exudate. The temperature by mouth was 96.8° F., pulse 68 and respirations 16. The heart was regular, not enlarged, and no murmurs were heard. The rest of the examination was essentially negative. The red cells numbered 5,760,000 with 95 per cent hemoglobin. Some of the red cells showed stippling and polychromatophilia, and a few normoblasts were seen. The white cells numbered 27,000 with 65 per cent mature polymorphonuclear cells, 5 per cent "stab" forms, 23 per cent lymphocytes, 6 per cent monocytes and 1 per cent basophiles. His injuries were not

serious, and no special attention was paid to him until the following afternoon, when it was noted that he appeared pale, cyanotic, and somewhat dyspneic. The neck veins were distended, the heart sounds were muffled, the ventricular rate was 40 and the blood pressure could not be obtained. An electrocardiogram taken at 5:30 p.m. showed complete auriculoventricular block with a ventricular rate of 40 and an auricular rate of 76. There was also an intraventricular conduction defect of the left bundle branch type (see figure 1).

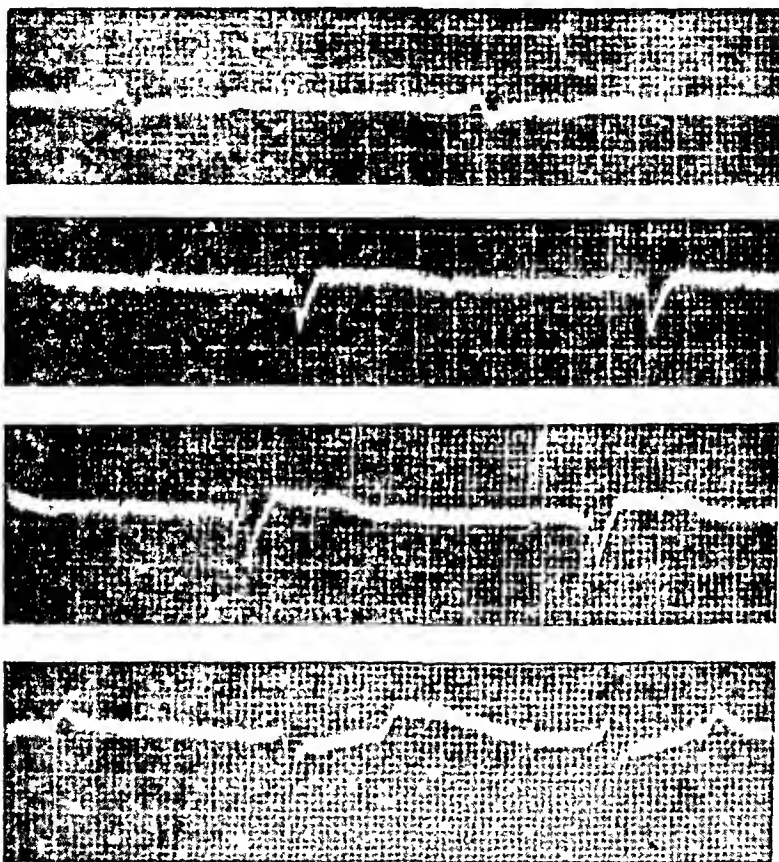


FIG. 1. Electrocardiogram taken Aug. 21, 1944 at 5:30 p.m.

The etiology of this severe cardiac condition was puzzling. There was no evidence of rheumatic heart disease and no history of exposure to any known toxin. The possibility of coronary embolus with closure of a vessel supplying the septum was considered. The possibility of diphtheria was also thought of, but the nose and throat appeared normal and the wounds did not appear infected. A direct smear of the abrasions of the buttocks showed considerable debris, a few pus cells, a few cocci, and a few bacilli which could not be identified. Culture of the abrasions was made on Loeffler's blood serum, and on the following day was reported as showing a pure growth of Klebs-Loeffler bacilli. These proved to be virulent to non-protected guinea pigs.

An electrocardiogram taken at 9:30 p.m. showed a complete heart block with a ventricular rate of 72. The ventricular complexes were bizarre and varied in duration from .25 to .42 sec. (figure 2), and this was interpreted as an agonal type of tracing. At 10:30 p.m. the patient suddenly became more dyspneic and cyanotic, and the neck

veins were markedly distended. Death occurred shortly after, approximately 32 hours after admission.

The necropsy was done by Lt. Col. Jesse E. Edwards. The heart weighed 440 grams. The ventricular myocardium appeared firm and deep red. The interventricular septum showed a patchy mottling. On microscopic examination there were seen in both ventricles and the interventricular septum large and small foci in which the myocardial fibers had disappeared leaving only stroma and a small infiltrate of lymphocytes, plasma cells, and macrophages. Portions of necrotic fibers still remained in most of these foci.

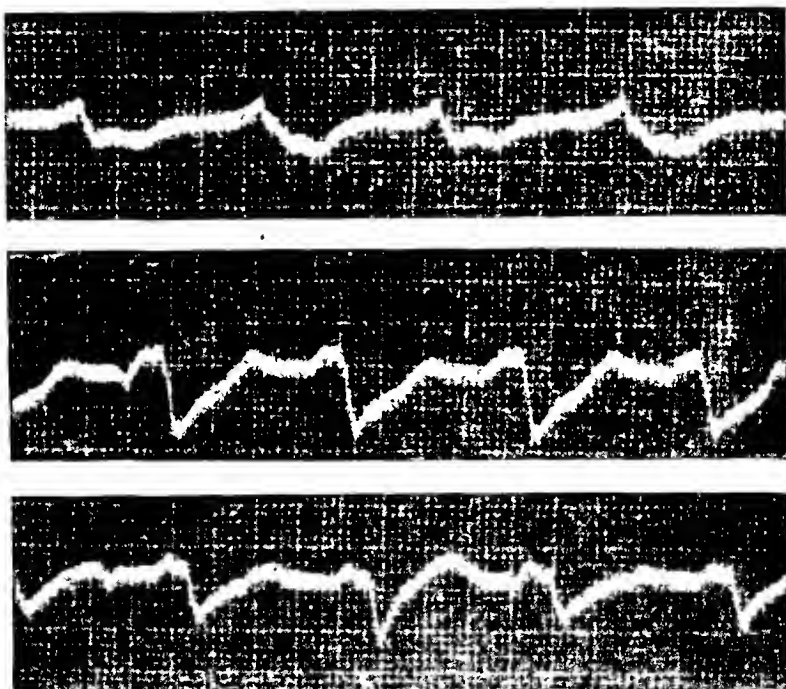


FIG. 2. Electrocardiogram taken Aug. 21, 1944 at 9:30 p.m.

A section taken from the infected abrasion of the buttocks showed denudation of the skin with a superficial but active cellular infiltrate of polymorphonuclear cells in the corium. There appeared to be very little fibrin in the exudate. Bacterial colonies were present on the surface and within the exudate. There was pulmonary congestion and edema of both lungs.

#### SUMMARY

A case is reported of cutaneous diphtheria with fatal toxic myocarditis. The diphtheritic infection was engrafted on what otherwise might have been trivial abrasions of the buttocks. The diagnosis was not established until after the patient's death. This failure may have been in part due to the fact that he passed through six installations during the course of his illness and did not remain long at any one of them. Moreover the lesion was not the characteristic deep diphtheritic sore, and no distinct membrane was ever noted. One should keep in mind the possibility of cutaneous and wound diphtheria even though the characteristic picture may not be present. Cultures of wounds and skin lesions

which fail to heal promptly should be a routine procedure. Prophylactically, the wearing of masks when dressings are done is advisable, since diphtheria infection is nearly always conveyed by droplets.

Cutaneous diphtheria was apparently rare on the Western front although reports of many cases have come from Africa, the Middle East and India. Early diagnosis is important because of the complications which the diphtheria toxin may cause. The commonest of these is peripheral neuritis, but the most serious complication, and by far the most common cause of death is toxic myocarditis. In view of this diphtheria antitoxin should be given as soon as the diagnosis is suspected. Delay is dangerous since once the toxin has been fixed in the peripheral nerves or myocardium antitoxin is of no avail.

*Addendum:* Since this report was written, we observed another case of cutaneous diphtheria in a patient with a shell wound near the left ankle. The wound developed thick rolled edges and a deep unhealthy base covered by a yellowish-gray membrane, which is the usual picture of wound diphtheria. Cultures and virulence tests were positive. The source of infection was not discovered. Throat cultures from the patient nurses, attendants and medical officers were negative. He received a total of 80,000 units of diphtheria antitoxin. No complications developed, and within a week the membrane disappeared and wound healing progressed uneventfully.

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#### VENTRICULAR TACHYCARDIA WITH ELECTRICAL ALTERATIONS RESULTING FROM DIGITALIS EXCESS\*

By J. H. CURRENS, M.D., *Boston, Massachusetts* and R. C. WOODARD, M.D., *Miami, Florida*

THE electrocardiographic picture of ventricular tachycardia is usually quite characteristic, and although the rhythm is as a rule slightly irregular, the ventricular complexes are quite uniform in appearance. Regular alternation in the direction of the QRS complexes during ventricular tachycardia has been reported by various authors, and, in the majority of cases digitalis intoxication has been responsible for the tachycardia.<sup>1-4</sup> We should like to present the following case report and electrocardiogram demonstrating alternation in the amplitude of the

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QRS complexes without an alternation in the direction of the complexes. This has the appearance of electrical alternans and is presented because of this unusual variety of ventricular tachycardia.

#### CASE REPORT

Mrs. C. A. W., a 75 year old married woman, was admitted to the hospital May 19, 1944 because of shortness of breath and dependent edema. For 20 years she had been troubled with recurrent arthritis of the fingers, knees and elbows, and this had resulted in slight deformity of the fingers, characteristic of rheumatoid arthritis. Eleven years before (1933) she was seen by Drs. Sprague and White in Boston who had made a diagnosis of aortic stenosis. She was started on digitalis at this time and has continued taking one tablet (0.1 gm.) each day. For five years mild diabetes mellitus had been present, and she had recently been taking 10 units of protamine insulin daily.

The patient was in good health and the cardiac reserve was quite good until five months before entry when she developed moderate dependent edema associated with some dyspnea which subsided spontaneously after one week of bed rest. Three weeks before entry the dependent edema reappeared, and dyspnea and orthopnea became bothersome. About 10 days before entry her digitalis dosage was increased to two tablets a day (0.2 gm.) in an effort to alleviate the dyspnea and edema.

Physical examination revealed a mild cyanosis of the face and lips, and the cervical veins were pulsating and moderately distended when the patient was erect. The heart was enlarged, and the apical impulse was in the sixth interspace in the anterior axillary line. The rhythm was totally irregular at an average rate of 95 except for short runs of regular tachycardia of short duration at a rate of about 145. There was a loud systolic murmur heard over the precordium, about equally well heard at the aortic and mitral areas but not well heard at the left lung base. No diastolic murmur was heard. The blood pressure was 160 mm. Hg systolic and 80 mm. diastolic. The liver descended four fingers' breadth, and edema was marked over the sacrum and lower extremities.

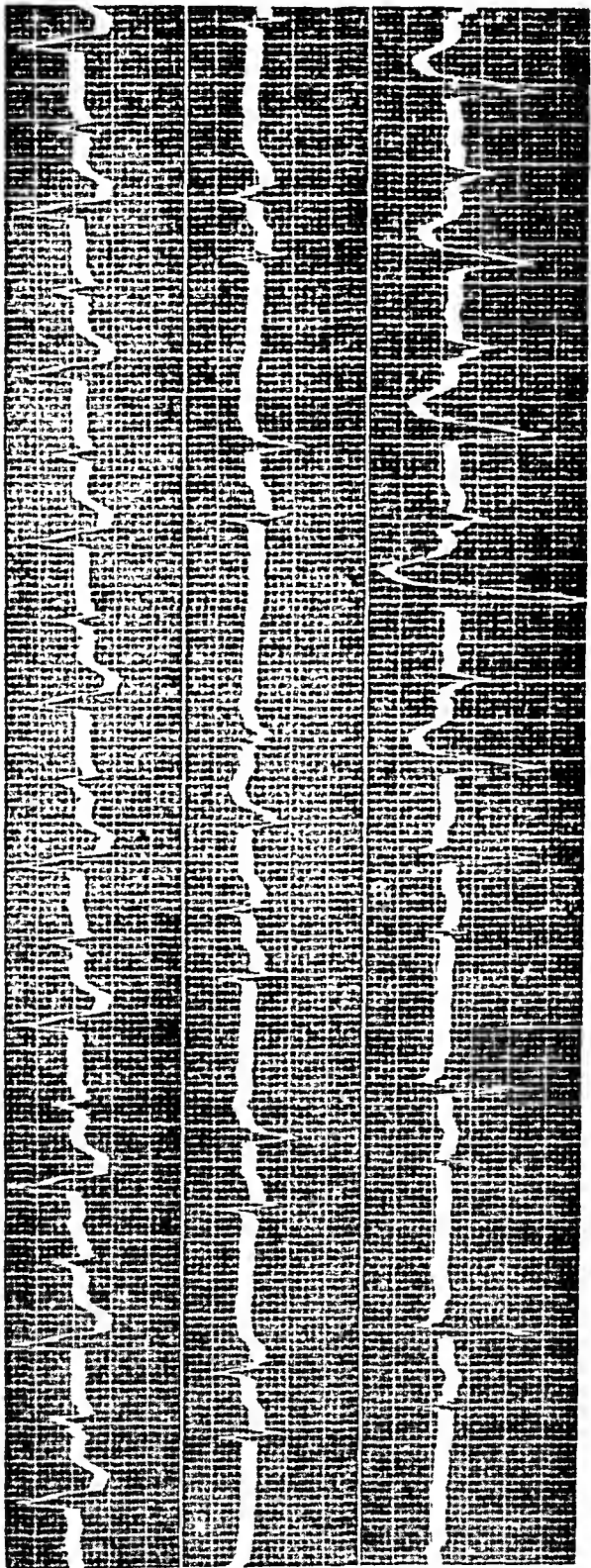
Laboratory data revealed normal blood counts, and the differential leukocyte count was likewise normal. Urinalysis revealed a two plus albuminuria but was otherwise negative. An electrocardiogram was made on entry and is illustrated in figure 1. It demonstrates auricular fibrillation with frequent ventricular premature beats and periods of ventricular tachycardia. Electrical alternans is present of varying degree during the ventricular tachycardia.

Digitalis was omitted, and 0.2 gm. of quinidine sulfate was given and repeated each six hours. The following morning pulsus bigeminus was present intermittently. No periods of tachycardia were observed, and at times there were periods when the extrasystoles were infrequent. Quinidine sulfate was continued in the same dosage and the patient was placed on ammonium chloride and a mercurial diuretic. On May 22, 1944 extrasystoles were still present although less frequent, and two days later no extrasystoles were present. Quinidine sulfate was then omitted. At no time did the patient complain of nausea, visual or mental disturbances. Digitalis was again resumed but in reduced dosage, the patient receiving 0.1 gm. five days a week. On May 27, the patient was discharged much improved, having lost about 10 pounds of edema fluid.

#### DISCUSSION

There is little doubt that the ventricular tachycardia in this case resulted from an excess of digitalis since it developed only after the dosage of digitalis had been increased and subsided following the withdrawal of the drug. The patient did





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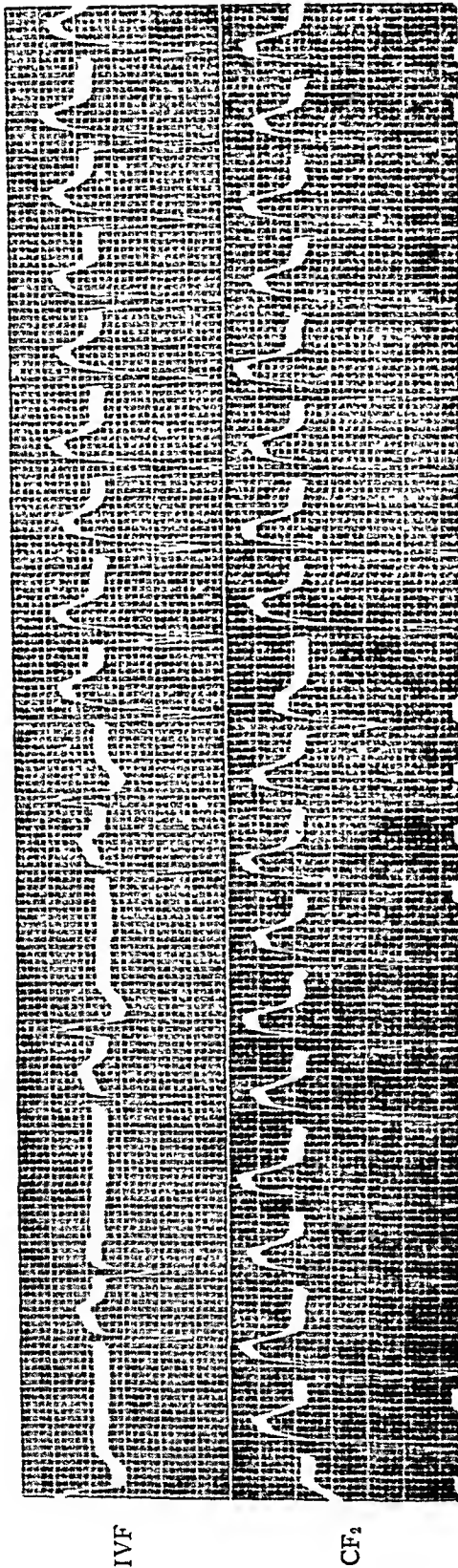


FIG. 1. The electrocardiogram taken on the day of entry to the hospital. Lead I demonstrates a tachycardia of 140 which is very slightly irregular and with alternation of the amplitude of the QRS complexes. The complexes are unidirectional and of equal duration (0.13 to 0.14 sec.). In Lead II, auricular fibrillation is present with fairly regular ventricular extrasystoles of two varieties and one short run of ventricular tachycardia of three complexes. In Lead III, the onset of ventricular tachycardia is seen with again the alternation in the amplitude of the complexes. In the two precordial leads, the usual type of ventricular tachycardia is seen with quite uniform contour of the ventricular complexes. The rhythm is slightly irregular. In Lead IV F, there are two types of ventricular extrasystoles as in Lead II before the onset of the ventricular tachycardia. A very slight electrical alternans is present in Leads IV F and CF<sub>2</sub> (1 to 2 mm.).

not, however, have any of the systemic symptoms of digitalis intoxication. The quinidine had a definite quieting effect upon the heart and reduced the duration and frequency of the paroxysms of ventricular tachycardia.

Although the QRS complexes in the electrocardiogram during ventricular tachycardia are usually fairly uniform, considerable variation of the complexes occurs in a few cases. When there is rhythmic variation of the complexes, it is most commonly an alternation in the direction of the ventricular complexes. The mechanism by which this odd type of pattern is produced is not clear. Palmer and White<sup>3</sup> listed five possible mechanisms: (1) alternating right and left bundle branch block; (2) alternating refractoriness of the large bundles of Purkinje fibers; (3) two separate foci; (4) reentry phenomenon and (5) a double ventricular circus movement.

Rhythmic variation during ventricular tachycardia other than the bi-directional type is exceedingly rare. Only one other recorded electrocardiogram of the reported cases at all resembled the electrocardiogram in the case presented here, and that was an unusual case of a 21 year old boy reported by Scherf and Kisch.<sup>5</sup> The ventricular tachycardia did not result from digitalis intoxication in their case. The complexes were unidirectional and varied in amplitude, form and duration of diastole.

In Leads I and III of figure 1, the variation is of amplitude and form of the complexes although the duration of diastole and intraventricular conduction remains uniform. This gives the appearance of electrical alternans. The duration of diastole is uniform in this case during the tachycardia which is in favor of the paroxysmal tachycardia having a single focus of origin. The alternating variation in the QRS complexes would then be explained by imperfect conduction through the Purkinje conducting system on alternate systoles, possibly a result of conduction fatigue during alternate systoles. The several types of ventricular extrasystoles demonstrated in Lead II of figure 1 indicate a high degree of irritability of the ventricular musculature.

The phenomenon of electrical alternans has been compared recently with pulsus alternans and is considered a sign of serious myocardial disease.<sup>6</sup> No doubt the bizarre type of electrical alternans presented in this case is similar in its origin and clinical implications to that of electrical alternans occurring in cases with paroxysmal auricular tachycardia. Although this patient survived the ventricular tachycardia, she died three months later from congestive heart failure.

#### SUMMARY

A case is reported in which alternation in amplitude of the QRS complexes occurred in the electrocardiogram during paroxysmal ventricular tachycardia resulting from excess digitalis therapy. This phenomenon has been compared with the electrical alternans occurring at times during paroxysmal auricular tachycardia and is considered a sign of serious but not necessarily lethal heart disease.

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## TRAUMATIC RUPTURE OF THE AORTIC VALVE: REPORT OF TWO CASES, ONE A PROVED AND THE OTHER A PROBABLE EXAMPLE OF THIS CONDITION \*

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EXAMPLES of rupture of the aortic valve by trauma or strain have appeared sporadically in the literature since 1830, when Plenderleath<sup>1</sup> reported the first case in the *London Medical Gazette*. An excellent and comprehensive review of the subject was made in 1925 by Howard,<sup>2</sup> who set himself the thankless task of combing the literature from 1830 to 1925 for reports dealing with this rare condition. He succeeded in finding 112 cases, 49 of which were proved by autopsy. A search of the literature from 1925 to the present has yielded seven more cases, including that of Howard, making a total of 119 cases, 58 of which were proved by autopsy. The present report is of two additional cases, one proved by autopsy and one as yet unproved.

### CASE REPORT

*Case 1.* I. G., a 50 year old male truck driver, was perfectly well until two weeks prior to admission to University Hospital June 2, 1939, when a load of fence posts fell onto him in the cabin of a truck he was driving, striking a heavy blow against his back and right shoulder. While straining to extricate himself from beneath the posts, he experienced a sudden pain and tightness in his chest. He became short of breath and this continued, with severe paroxysms of dyspnea at night, up to the time of his admission. He was seen by Dr. Robert S. Ballmer of Midland, Michigan soon after the accident and the peculiar character of the physical signs was appreciated and the probable diagnosis was suspected by him. Digitalization had been completed and he was receiving aminophyllin 0.1 gm. three times daily before he came to the hospital.

The past history was not contributory. He had never been sick and denied venereal disease.

Physical examination revealed a well developed and nourished white male of 50 years in acute respiratory distress. The temperature was 98.6° F., the pulse 80 per minute, and respirations 24 per minute. The blood pressure was 175 mm. Hg systolic and 55 mm. diastolic. The pupils reacted normally to light. The ocular fundi showed some arterio-venous nicking and there was definite pulsation of the retinal arteries.

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Chest expansion was free and equal on both sides, but resonance was impaired over both lung bases posteriorly. Fine, moist râles could be heard as high as the inferior borders of the scapulae. The heart was enlarged with the left border of cardiac dullness 13 cm. to the left of the mid-sternal line in the sixth interspace. The point of maximum impulse was lateral to the nipple and there was definite evidence of over-activity of the heart. A diastolic thrill could be felt in the aortic area, and in this region a loud, buzzing early diastolic murmur could be heard. It had a definitely

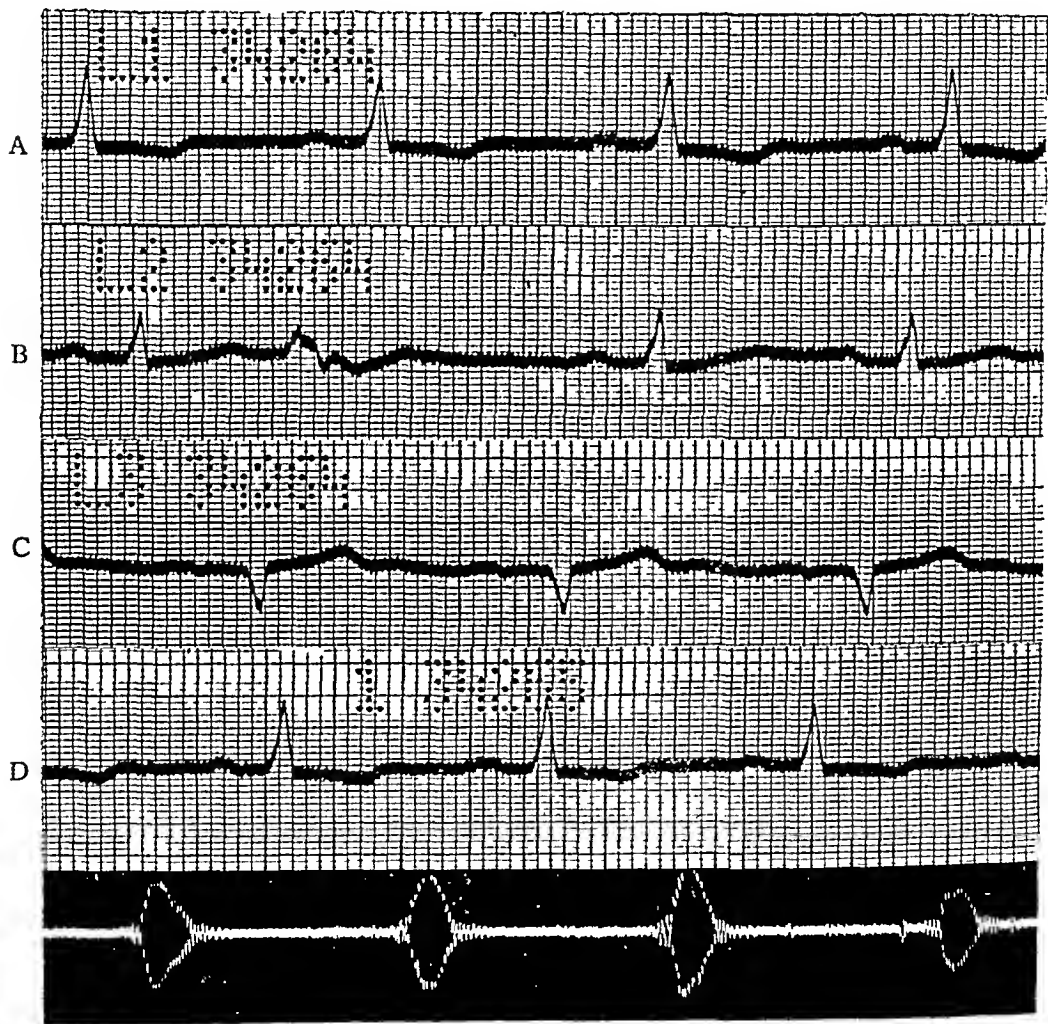


FIG. 1. Records from Case 1. A, B, and C show standard Leads I, II, and III. There is slight left axis deviation and inverted T-waves are present in Lead I. One ventricular premature beat is seen. D shows a sound tracing (below) taken over the upper sternum simultaneously with Lead I. The regular character of the oscillations indicates the musical character of the aortic diastolic murmur.

musical quality, could be heard over the entire precordium and much of the thorax, and was transmitted well into the neck vessels. Abdominal examination was unsatisfactory because the patient was unable to lie down. The liver was not felt and no masses were present. The extremities showed pitting edema of the feet and ankles. The nail-beds were cyanotic.

The blood Kahn test was negative. The hemoglobin was 89 per cent; the red blood count was 4,050,000 and the white blood count 9,000. These values, as well as

the differential counts varied, as might have been expected, during his hospital course. A series of chest roentgen-rays traced changes in the heart and lungs from admission until two days before his death. At no time were the lung fields free of congestion, and in the later films pulmonary consolidation of the right lower and middle lobes was seen, as well as a right pleural effusion. Electrocardiograms and sound tracings over the base of the heart were made and are shown in figure 1.

In spite of the usual treatment for congestive heart failure and complicating pulmonary infection, the patient failed to improve significantly and died on the fifty-fifth day of hospitalization approximately 69 days after the original trauma.

A summary of the relevant autopsy findings follows: The cardiac apex was 13 cm. to the left of the mid-sternal line at the level of the sixth interspace. The pericardium was slightly distended but showed no other abnormality. The heart was enlarged and weighed 650 grams. The apex was markedly broadened in comparison with the normal. Both ventricles and auricles showed hypertrophy and dilatation. The wall of the left ventricle measured 14 mm. in thickness. The endocardium was smooth and shiny throughout. The mitral valve was normal except for terminal dilatation. The aortic valve showed a transverse rupture, 1 cm. in length along the line of the insertion of the right anterior and posterior cusps and including the commissure, thus allowing the cusps to prolapse downward into the ventricle and the commissure to move away from the wall of the valve ring. The right ventricle showed dilatation but was not abnormal in other respects. The pulmonic and tricuspid valves were normal. The coronary ostia were normally located and showed only slight atherosclerosis.

*Case 2.* R. H., a boy of 11 years, was in good health until eight months prior to his visit to University Hospital on November 13, 1945, when his mother took him to a competent pediatrician because of a digestive upset. At this time no cardiac abnormality was found. Six months later his mother, who chanced to be sleeping with him, heard a peculiar noise in his chest. She took him to his doctor who detected a heart murmur. At this time the boy had no unusual dyspnea, chest pain, or other cardio-respiratory symptoms, but did state he would fatigue rather easily on moderate exertion. He gave no history of rheumatic fever or other serious illness in the past and was not a blue baby. On initial questioning no history of trauma was elicited. Later, however, the boy's father returned and volunteered the information that several months previously, while boxing with his son he had landed a solid blow on the boy's chest, which floored him and knocked the wind out of him. He complained of no pain or other symptoms, however, and shortly afterward seemed all right. There had been no other trauma.

Examination revealed a rather large male child of 11 years who appeared to be in good health. The blood pressure was 130 mm. Hg systolic and 20-0 mm. diastolic. There was rather marked systolic arterial pulsation in the supra-sternal notch and above the clavicles. The lungs were clear. The heart was moderately enlarged, with the left border of cardiac dullness just inside the left anterior axillary line. The heart rate was approximately 80 per minute, and there was no arrhythmia. A diastolic thrill was felt in the aortic area and down the left border of the sternum. In this region, a very loud, musical, early diastolic murmur was heard. No other murmurs were audible. The pulses were of the Corrigan type and Duroziez's sign was present.

Electrocardiograms and sound tracings taken over the base of the heart were made and are shown in figure 2.

## DISCUSSION

As noted by previous writers, the majority of instances of rupture of aortic valves occur in valves that were previously diseased or abnormal. Plenderleath,<sup>1</sup>



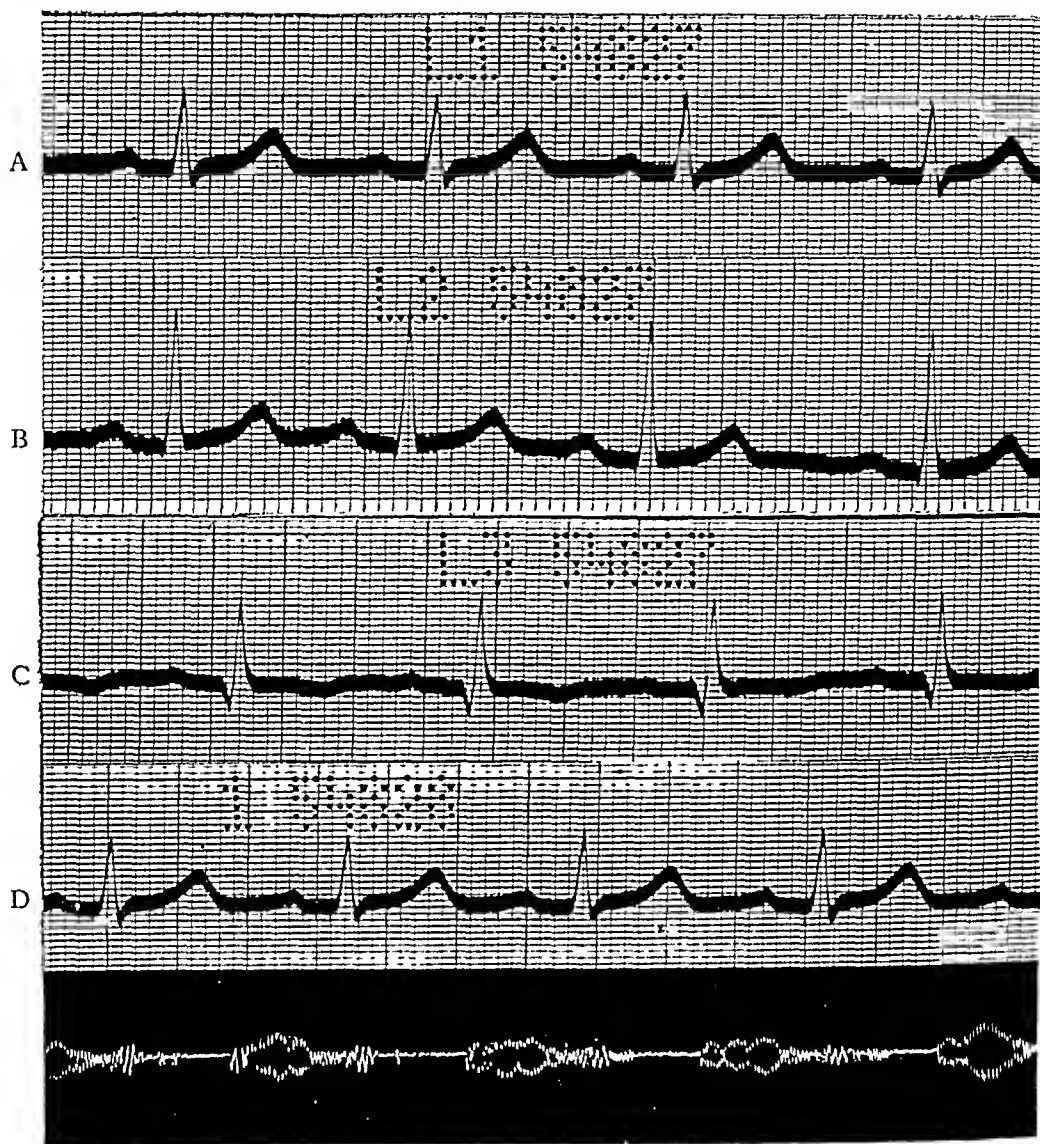


FIG. 2. Records from Case 2. A, B, and C, the standard leads, are well within normal limits. D shows a sound tracing taken over the upper sternum, simultaneously with Lead I. It indicates the musical character of the aortic diastolic murmur.

in reporting the first proved case in 1830, described the valves as "thickened red, and in the tendinous margin loaded with calcareous matter." Porter,<sup>6</sup> in 1931, had the unusual experience of hearing an aortic valve rupture as he was listening to the heart of a patient with acute gonococcal endocarditis. In this case, rupture was followed immediately by fatal edema of the lungs. A smaller number of cases have been reported of rupture of previously normal valves. The case reported by Kissane et al.<sup>3</sup> in 1936 was such an instance, the patient having been examined by the authors before the rupture occurred. Of the two cases here reported, the first was an instance of rupture of a normal valve. The valve in the second case had also been found normal in a previous examination, but the possibility of a congenital anomaly such as bicuspid valve cannot be excluded.

The presence of a very loud musical aortic diastolic murmur, particularly in individuals in whom trauma has occurred and previous examinations have revealed no murmur, should always suggest rupture or perforation of the aortic valve.

### SUMMARY

Two cases of traumatic rupture of the aortic valve are presented. In one case, the antemortem diagnosis was confirmed by necropsy, whereas, in the second patient the history and the physical findings appear to justify a presumptive diagnosis of this condition.

The author wishes to express his appreciation to Dr. F. D. Johnston for help in the preparation of this paper.

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## DIAPHRAGMATIC SPASM ASSOCIATED WITH RECURRENT LEFT PNEUMOTHORAX \*

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As early as 1832 a report on "diaphragmatic convulsion" was described by Merat.<sup>1</sup> Since that time there have been a considerable number of cases of spasm of the diaphragm reported in the literature. None of these was verified by roentgenograms or fluoroscopy. In 1916, two cases were described by Simonin and Chavigny,<sup>4</sup> one associated with tuberculosis and the other following trauma of the chest. These were proved by fluoroscopy. Since that date a small number of cases have been described which were verified by fluoroscopic examination. Most of these were apparently sequelae of encephalitis.<sup>8, 9, 11, 13, 15, 16, 17, 21</sup> Other cases were attributed to surgical abdominal conditions,<sup>17</sup> such as intestinal obstruction with repeated laparotomies,<sup>27</sup> the presence of a cervical rib,<sup>8</sup> a fracture of the xiphoid process<sup>12</sup> and even pregnancy.<sup>24</sup>

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There is some confusion in the literature because of the use of various terms to describe diaphragmatic disturbances. The terms "convulsion," "tic," "spasm," "flutter," and "pleurodynia" have all been used. We suggest the term "spasm" be used with the modifier, "tonic" or "clonic" as indicated by the characteristics of the case. Its use in this way would be adequate for all instances except epidemic pleurodynia, which is a separate disease entity.

Spasm of the diaphragm as reported in most cases involved clonic contraction of one or both leaves of the diaphragm. In these cases the diaphragm contracted and relaxed at 100 or more times per minute and thus appeared to "flutter." These clonic spasms either disappeared spontaneously or finally required phrenic exeresis for relief.

Whitehead, Burnett, and Lagen <sup>26</sup> in 1939 described a case of "diaphragmatic flutter" with symptoms suggesting angina pectoris. In this case, pain was precordial and radiated down the left arm. It was severe, related to emotional stress and was diagnosed as hysterical. Phrenic nerve resection gave only temporary relief. On fluoroscopy, both leaves of the diaphragm were found to flutter at a rate of 200 vibrations per minute. No evidence of organic disease was found, and attacks recurred several times during a five year period.

In a case with intestinal obstruction, Handron <sup>27</sup> suggested that adhesions following repeated abdominal operations might be responsible for the diaphragmatic "tic." Following a fifth laparotomy for intestinal obstruction, his patient experienced severe pain in the left scapular area and left upper abdomen. It occurred in attacks which were sometimes precipitated by eating. Clonic spasm of the left diaphragm at the rate of 125 vibrations per minute was proved by fluoroscopy. Each attack was accompanied by hyperventilation, alkalosis and mild tetany. It was characteristically relieved by dilaudid and bilateral phrenic resection gave complete relief.

In a case described by Skillern <sup>15, 21</sup> of "tic" or clonic spasm of the diaphragm occurring after encephalitis, the patient experienced a fluttering sensation, but there was no pain. Repeated phrenic nerve interruptions resulted in each case in only temporary relief. Complete exeresis bilaterally was finally required for relief of the patient's symptoms.

Joannides <sup>20</sup> in 1935 described a case of acute primary diaphragmitis (Hedblom's syndrome). This is simply acute pain in the right abdomen occurring when the diaphragm is irritated by pneumonia or perforated ulcer. There is no spasm involved, however, except that commonly seen in protective splinting of the chest. Kulenkamp,<sup>10</sup> Roemheld,<sup>18</sup> and Lurje and Stern<sup>14</sup> described a slightly different condition in which diaphragmatic pain occurred as a result of pressure when the stomach was distended by air. This syndrome lacks the evidence of spasm or diaphragmatic dysfunction and hence is not related to the present discussion.

#### CASE REPORT

The patient was a 26 year old captain. His health had been excellent until January 1944 when he developed an acute upper respiratory infection with considerable coughing. The cough, largely non-productive, persisted throughout February and March. On March 17, while coughing he developed a severe pain in his left lower chest which radiated to the left shoulder. Roentgenologic examination revealed a left pneumothorax with about 10 per cent collapse. The lung promptly reexpanded,

and the patient's cough disappeared. However, a dull aching pain in the lateral aspect of the left lower chest was noted which was persistent but did not interfere with his duties. While sitting at his desk on July 23, 1944, he experienced an acute pain similar but more severe than that occurring in March and associated with a sensation of breathlessness.

On admission to this hospital on August 24, 1944, the results of physical examination were entirely negative except for the usual signs of pneumothorax. Roentgen-ray revealed a partial left pneumothorax. Repeated sputum examinations including guinea-pig inoculation with gastric washings failed to reveal the presence of acid-fast organisms. The tuberculin test was negative. Blood counts and sedimentation rates were normal. The lung slowly reexpanded, but the patient continued to have an aching pain in the left lower chest. Early in December 1944, this chest pain, which was present daily, became more severe and began to occur in acute attacks. It originated in the left lower antero-lateral portion of the chest and radiated over the crest of the left shoulder. It occurred spontaneously but was also noted whenever the patient coughed, breathed deeply, changed position or exercised. Exercise initiated sharp knife-like pain in this area which was best described as "spasms of pain" occurring 10 to 30 times per minute, making it difficult for the patient to breathe and so severe that opiates were needed for relief. These attacks awakened the patient from sleep. The characteristics of this pain and its precipitating factors were indistinguishable from those described as occurring in pleurodynia. The patient walked in a stooped position favoring the left side. There was no evidence of recurrence of the pneumothorax. Observation of the patient's thoracic wall during an episode of this pain revealed the presence of marked tonic contractions of the muscles of the left lower chest and left upper abdomen. Fluoroscopic examination while this pain was in progress visualized tonic spasms of the diaphragm which coincided with the severe episodes of pain.

A novocaine block of the left phrenic nerve was contemplated, and the patient was transferred to a hospital designated as a center for diseases of the chest. However the frequency and severity of the attacks subsided gradually and spontaneously, and this procedure was not carried out. By the end of a three-month period, the patient was symptom free.

#### COMMENT

We have been unable to find any other case in the literature in which diaphragmatic tic has occurred as a sequel to pneumothorax, either spontaneous or induced. This is particularly unusual in view of the large number of cases in which artificial pneumothorax has been induced. The case we have described differs from other cases of "flutter" or "tic" since the spasm was tonic rather than clonic or "fluttering", and was associated with pain rather than the feeling of flutter. It may be that some of the reported cases were characterized by tonic contractions, but none was so described. The few cases of painful "tic" described all showed flutter fluoroscopically. On the other hand, all but a few of the cases of "flutter" reported were postencephalitic and were not associated with pain.

An interesting observation was the fact that position and exercise apparently played a trigger rôle in initiating attacks of diaphragmatic spasm and pain. Although this case cannot be described as one of epidemic pleurodynia, it is remarkable that the type of pain, its location, the postural factor and the precipitating factors were identical to those described for epidemic pleurodynia.<sup>81</sup> Likewise, all other cases of diaphragmatic dysfunction both with and without pain

have been associated with rapid clonic spasm or flutter instead of a *tonic* spasm as was noted in our case. In this respect it further mimicked epidemic pleurodynia.

### SUMMARY

A case of *tonic* contraction of the diaphragm is described, presumably due to spontaneous pneumothorax, and various considerations in regard to various dysfunctions of the diaphragm are discussed.

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### ADRENALIN PRODUCING TUMOR (PHEOCHROMOCYTOMA) CONTAINING 2300 MG. OF ADRENALIN\*

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PHEOCHROMOCYTOMA, the "physiologically malignant"<sup>1</sup> and histologically benign adrenal medullary tumor produces a clinical picture almost identical with that produced by large doses of epinephrine.

One hundred and fifty cases have been reported. The increasing frequency of antemortem diagnoses, particularly in the last decade has shown that the rarity of this clinical syndrome is more apparent than real. Because of the demonstrated effectiveness of the surgical treatment it is important that physicians be aware of this pathologic entity and the methods of assuring a correct diagnosis. Forty-one of the 150 cases have been treated surgically since the first operation by Charles Mayo in 1927.<sup>2</sup> Seventy-five per cent have been cured. Successful removal has been accomplished in patients ranging in age from 16 months to 65 years.<sup>3, 4</sup>

We report a case which we have studied comprehensively. We feel that it has several peculiarities which justify its report—viz., bilateral adrenal tumors, associated metastatic carcinoma of the thyroid, and the relatively simple confirmatory tests made to substantiate the clinical diagnosis.

The syndrome associated with pheochromocytoma is characterized mainly by acute unpredictable attacks lasting from a few seconds to several hours. In a typical attack there is sudden cardiac palpitation with either an increase or decrease in pulse rate (depending on the reflex mediated via the carotid sinus pressor mechanism) and a very marked rise in the blood pressure.<sup>5</sup> The patient notices a feeling of fullness in the throat and choking, and perhaps fullness, pressure, pain or burning beneath the sternum and in the epigastrium. There are often noted tingling and blanching of the extremities and tip of the nose together with pallor and generalized sweating. The pallor is followed by flushing. The patient characteristically feels nervous or anxious, tremulous and weak and has a headache, vertigo, blurred vision, mydriasis and perhaps tinnitus

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and air hunger. Polyuria is common and gastrointestinal symptoms such as sialorrhea, nausea, vomiting, colic and diarrhea are not infrequent. Epiphora is often noted. Other objective manifestations are angiospasm in the ocular fundi, glycosuria, albuminuria and hyperglycemia. Unusual susceptibility to surgical shock and pulmonary edema are also characteristic.<sup>6</sup>

Cases have been reported in which hypermetabolism was the outstanding clinical finding.<sup>7, 8</sup>

### CASE REPORT

A. M. M., a 39 year old white woman, married and without children, was admitted to the Indiana University Medical Center on October 24, 1944. Her only complaint was persistent profuse sweating.

She was born in Nebraska and had lived in the southern states most of her life. For the 10 years before admission she had been a laboratory technician in Federal laboratories, testing bovine and caprine blood for "Bang's disease."

The patient had severe chorea when she was 14 years old. At that time she was hospitalized for three months and was released following a tonsillectomy. She was in good health thereafter until 1938, when she developed weakness, palpitation, tachycardia, nervousness, and a tendency to fall over on stooping. A right hemithyroidectomy was done for relief of these symptoms. She remained well until 1942.

Early in 1942 a pain in the right lower quadrant led to a right oöphorectomy, salpingectomy and appendectomy.

In the summer of 1942 the attacks of profuse sweating began. These were so severe that her clothes often became saturated in a few minutes. The attacks at first were mild but they gradually increased in frequency and severity. She began to have a new form of attack. These new seizures were first noticed in the summer of 1943. She attached no importance or significance to these symptoms. They were often initiated by emotional strain—one followed the sudden return of a brother from the armed services—by pressure of work, carrying heavy objects, and sometimes there was no apparent cause. Rarely the attacks would awaken her. These attacks had no definite relationship to her profuse drenching sweats. She referred to these attacks as "the jitters." The typical "jitters" attack would begin with a dull, "cramping ache" and feeling of fullness in the pelvis and quickly radiated upward to the region of the costal borders. This was either accompanied or preceded by pain and tenderness in an enlarged lymph node located one inch below the mastoid. Nausea and non-projectile vomiting would follow. The vomiting in the severe attacks was attended by involuntary emptying of the bladder. Her scalp would "tingle" as though the hair was standing on end. She would become "jittery and shaky." Tachycardia, extremely active precordium, dyspnea, and orthopnea occurred a few minutes after the vomiting ceased. Her attitude was one of extreme fright. She had a noticeable exophthalmos and scleral injection. Vision would become blurred and the patient complained of a twitching sensation in her eyes. Her face would take on a waxen pallor and mottled appearance. Circumoral pallor and cyanosis of the lips were present at the height of the attacks. After "the jitters" were over she was completely exhausted and very warm. The attacks lasted several minutes to several hours. On no occasion prior to this hospital admission was her blood pressure taken during an attack. Her local physician told her previously that she had a mild hypertension.

In November 1943, the patient suffered pain in the left loin. Medical consultants made a diagnosis of kidney disease and the patient was given sulfonamide therapy for a period of three days. A remission of symptoms followed.

She had no other illnesses of importance. Blood pressure taken by one of us before hospital admission was 174 mm. Hg systolic and 100 mm. diastolic.

*Physical Examination.* The patient was healthy in appearance and looked younger than her stated age. She was well developed and well nourished and was sweating profusely. She was calm and deliberate throughout her entire examination. Weight was 105 pounds (47.7 kg.), height 4 feet, 11½ inches, temperature 99° F., pulse rate 95, respirations 16 per minute and blood pressure 164 mm. Hg systolic and 110 mm. diastolic. The skin surfaces revealed many scattered sudamina and mild eczematous areas in the regions which were most moist. Hair distribution over the body was of the normal female type. The temporal and radial vessels were normal. Perspiration extended well back into the scalp, and the hair was moist and oily. The eyes reacted well to light and accommodation. Extra-ocular movements were normal; pupils small, round and equal. No noticeable exophthalmos was present. Ophthalmoscopic examination was entirely normal with the exception of slight tortuosity of the arteries of the fundus oculi. There was no visible sclerosis and no evidence of any hemorrhages. The neck showed no extraordinary pulsations. A firm, enlarged node was found one inch below the mastoid bone on the right. A transverse thyroidectomy scar was present. The heart was not enlarged. A well transmitted, soft systolic blowing murmur was heard over the base of the heart. The abdomen was normal with the exception of a mass, firm and somewhat tender, high in the upper right quadrant. The mass was easily demonstrated on deep palpation when the patient took a deep inspiration. Reflexes were normal. Neurological, pelvic and rectal examinations were without abnormal findings.

There was nothing significant in the family history.

*Laboratory Examination.* Hemoglobin 13.0 gm., red blood cells 4.6, white blood cells 7,750 with a normal differential count. Bleeding time 2 minutes; coagulation time 1 minute, 25 sec. Urinalysis revealed a sp. gr. of 1.010 to 1.021. No albumin and no sugar were present. Blood sedimentation rate was 25; hematocrit was 50.5 per cent vol. packed cells. Mazzini flocculation test was negative. There were no agglutinations for *E. typhosus*, O and H antigen, para-typhosus, A and B antigen, and *Brucella abortus* antigens. Blood chemical studies revealed non-protein nitrogen 36 mg. per cent; fasting blood sugar was 83 mg. per cent; serum cholesterol was 343 mg. per cent and cholesterol esters 242 mg. per cent (Bloor method). Serum chloride (NaCl) was 631 mg. per cent. Serum protein was 7.10 mg. per cent; serum albumin 5.68 gm. per cent and serum globulin 1.42 gm. per cent. Twenty-four hour urine specimen sodium chloride was 700 mg. per cent, chlorine 420 mg. per cent. An oral glucose tolerance test revealed a fasting blood sugar of 107 mg. per cent with a negative urine sugar. One-half hour after ingestion of 100 gm. of glucose, the blood sugar was 164 mg. per cent. One hour following ingestion the blood sugar was 200 mg. per cent with 0.8 per cent urine sugar. Two hours after beginning the test, blood sugar had dropped to 138 mg. per cent and the urine showed 1.6 per cent sugar. Phenolsulphonephthalein test revealed 27 per cent excretion in 15 minutes and 39 per cent excretion in 30 minutes. Urea clearance test was 71 per cent of normal. Blood urea nitrogen per 100 c.c. was 17.6 mg. Urea index was 56. Serum sodium chloride was 620 mg. per cent. Basal metabolic rate varied from +56 to +74 on three separate days.

Once the diagnosis of pheochromocytoma is suspected from clinical manifestations, special diagnostic procedures are necessary for proving or disproving it and also for localizing the tumor if one be present. The procedures which we present here are for the most part simple enough to be carried out as office procedures if the proper precautions are taken to prevent the artificially induced attacks from reaching a maximum.

Perirenal pneumograms have been done in a large series of cases but are not

without danger and should be avoided by those having limited experience with this technic.<sup>9</sup>

Radiographic evidence corroborated our physical findings of a mass in the right hypogastrium.

*Roentgen-Ray Examinations.* "The depression of the superior calyx of the right kidney together with a suggestion of a mass overlying the superior pole of this kidney supports the possibility of there being a tumor of the right adrenal gland. The roentgen-ray studies of the skull show findings which appear to be within normal limits. Chest roentgen-ray is normal."

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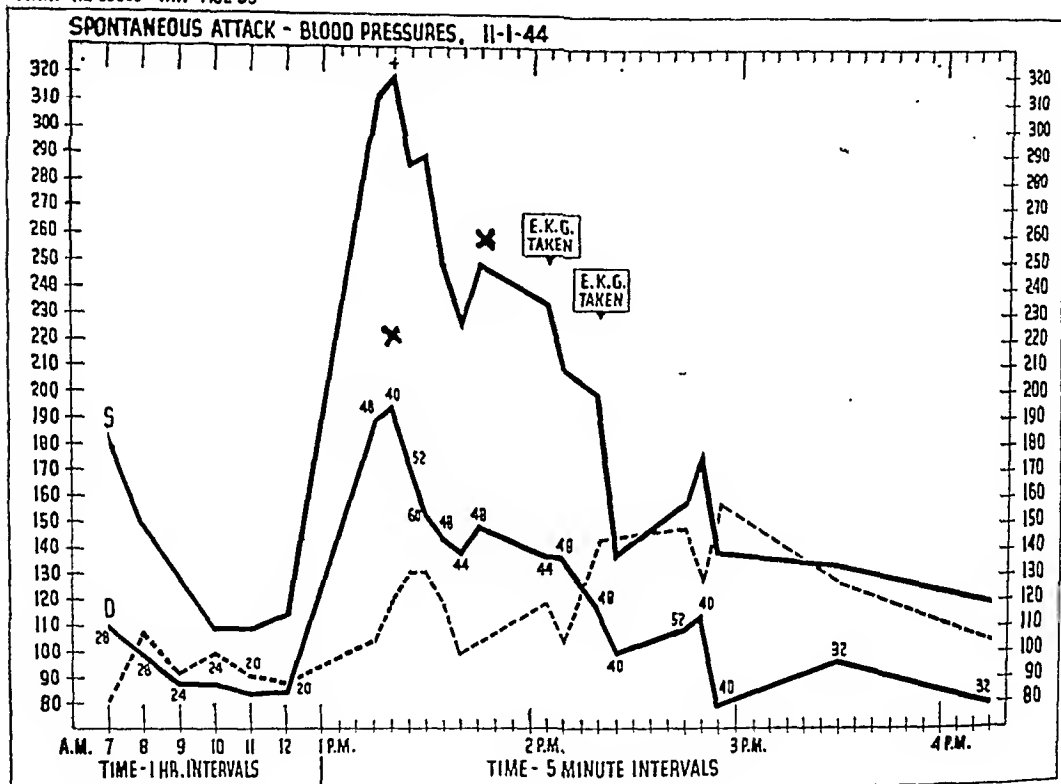


FIG. 1. Spontaneous Attack.

S = Systolic blood pressure.

D = Diastolic blood pressure.

The broken line represents the pulse rate.

Arabic numerals along line D = respirations per min.

Note time intervals.

*Typical Spontaneous Attack* (Figure 1). The onset followed the noon meal by one hour and came after four normal hourly blood pressure readings. The patient was lying on her back in bed when she was suddenly struck by a "twisting pain in the lump in the right side of the neck" (lump = lymph node one inch below mastoid process). At the same time a "lump" which started at the symphysis pubis moved up the midline to the costal margin. Nausea with vomiting of undigested food and involuntary emptying of the bladder lasted for about minutes.

Eyes: There was scleral injection, exophthalmos and a subjective complaint of "twitching feeling in back of eyes." There was circumoral pallor, a cyanotic tinge to the lips, and general waxen pallor especially noticeable over the face. The patient

also complained of a "drawing feeling" over the scalp. She then had profuse sweating, generalized except for the lower extremities. The knees had a mottled purple hue. She remarked that "legs ache, and hands and arms have a tingling feeling like an electric shock, and goose pimples all over." Weakness and exhaustion followed the fall in blood pressure. Dyspnea was common throughout. There was orthopnea during the vomiting attack. Severe coughing followed the onset by one and one-half hours. Subjective complaints lasted only 20 minutes after the onset. Blood pressure had returned to base line in two and one-half hours.

During this attack gr. 1/150 nitroglycerine (sublingual) was used twice in an attempt to abort the alarming pressure of 320 mm. Hg systolic and 195 mm. diastolic. (Pressure above 320 could not be recorded because of the limitations of the manometers available.) Nitroglycerine administered at "X" in figure 1.

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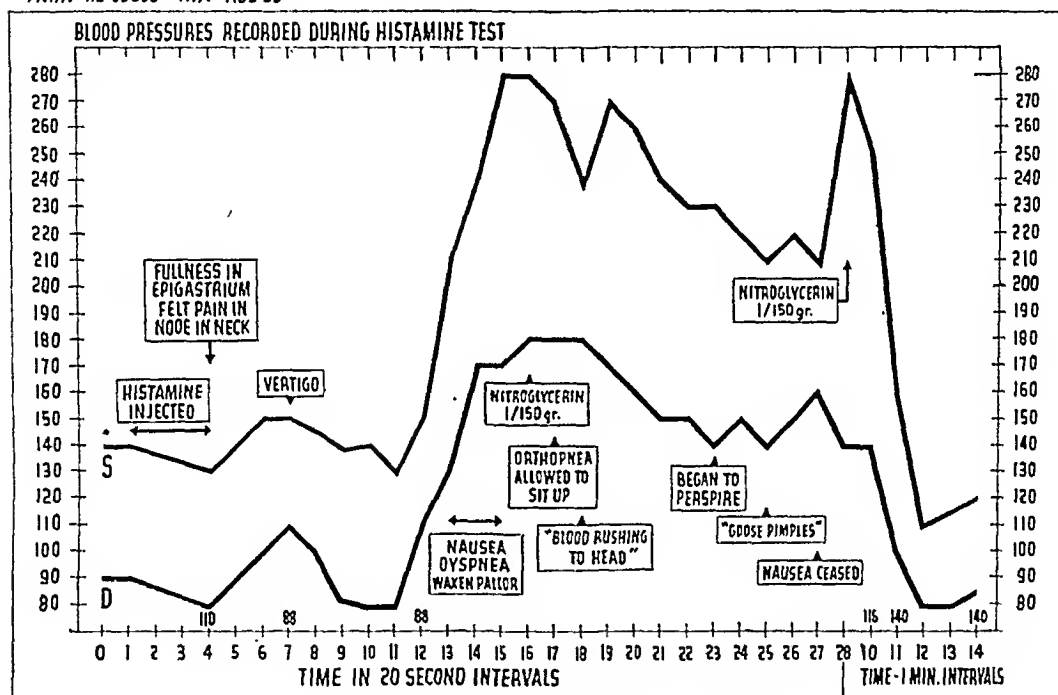


FIG. 2. Histamine Induced Attack.

Time intervals 20 seconds.

D = Diastolic blood pressure.

S = Systolic blood pressure.

An electrocardiogram taken approximately one hour after onset of the attack showed the P-wave peaked in  $L_1$  and  $L_2$ , inverted in  $L_3$ .  $T_1$  was diphasic but upright in  $L_2$ ,  $L_3$  and  $L_4$ . Left axis deviation was more marked than during normal periods. Rate was 150. Normal sinus rhythm and normal conduction times were present.

Oscillometric readings varied between 0-5. Normal readings on this patient 1-1.5 in same region over calf muscles.

Repeated trials to induce an attack by changes in position failed.

Adrenalin was not used in an attempt to produce an attack because of the severity of the symptoms.

*Histamine Induced Attack* (Figure 2). Personal communication by one of us (J. O. R.) with Dr. Grace M. Roth and a case report from the Mayo Clinic led to the



use of a very simple test which Dr. Roth has devised for the study of epinephrine producing tumors. The pharmacological and physiological aspects of this are not clearly understood.<sup>10, 11</sup>

One cubic centimeter of histamine acid phosphate containing .025 mg./cu. cm. was used as test material. One-tenth of this material was injected I.V. No untoward reaction was noted after 30 seconds, and the remainder was then introduced by the intravenous route. (See figure 2 for graphic representations.)

The blood pressure fell slightly and then began a gradual rise to slightly above the average base-line . . . again there was a slight fall to the base line which was immediately followed by a very sudden and alarming rise to 280 mm. Hg systolic and 180 mm. diastolic. This took place four minutes after histamine introduction. Blood pressure was taken every 20 seconds throughout the experiment. The patient complained of vertigo, fullness in the epigastrium, and pain in the node in the neck before any rise in blood pressure was noted.

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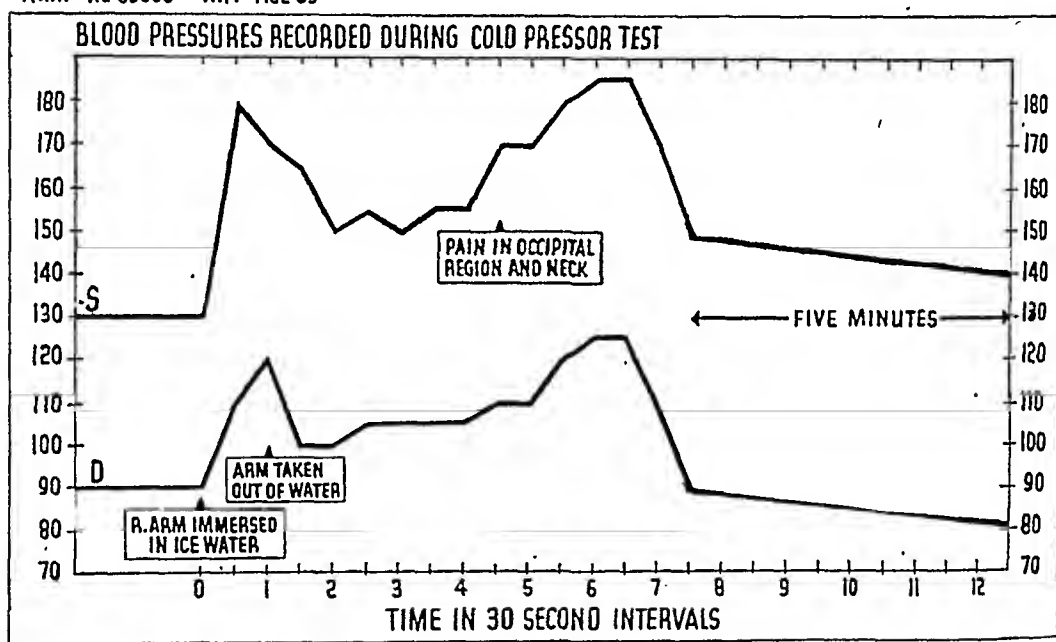


FIG. 3. The Cold Pressor Test.

S = Systolic blood pressure.

D = Diastolic blood pressure.

As soon as the blood pressure reached 280 mm. Hg systolic and 180 mm. diastolic the patient was given nitroglycerine 1/150 gr. She complained of severe dyspnea, nausea, "blood rushing to head," orthopnea and "cold." Her eyes had a terrified look. Exophthalmos was noted. Scleral injection was present. Dilatation of pupils was not noted. There was a circum-oral pallor, cyanosis of the lips and "splotched" appearance of the skin over the face and knees. The skin was cool and soon became covered with "goose pimples." The patient said that she could feel her hair standing on end. Approximately two minutes after sublingual administration of nitroglycerine the blood pressure began to fall but took another sharp rise in the next minute. The rise was again aborted with nitroglycerine. Blood pressure returned to base-line two minutes later, i.e., 12 to 13 minutes after administration of the test solution.

*The Cold Pressor Test* (Figure 3). The blood pressure prior to this test showed an average level of 130 mm. Hg systolic and 90 mm. diastolic. The sphygmomano-

meter was applied to one arm and the other arm was immersed in ice water. In 30 seconds the blood pressure had risen to 180 mm. Hg systolic and 120 mm. diastolic. The arm was removed from the ice water in 60 seconds and the pressure began to return to a normal level. In 3½ minutes a secondary rise began. It reached a peak of 185 mm. Hg systolic and 120 mm. diastolic, six minutes after the experiment was begun, and remained at this peak for 1 minute then returned to normal two minutes later.

*Massage over Tumor Area* (Figure 4). Active and passive changes of the patient's position had been unsuccessful in precipitating attacks. In an attempt to produce an attack the mass overlying the upper pole of the kidney was massaged vigorously for 10 to 15 seconds.

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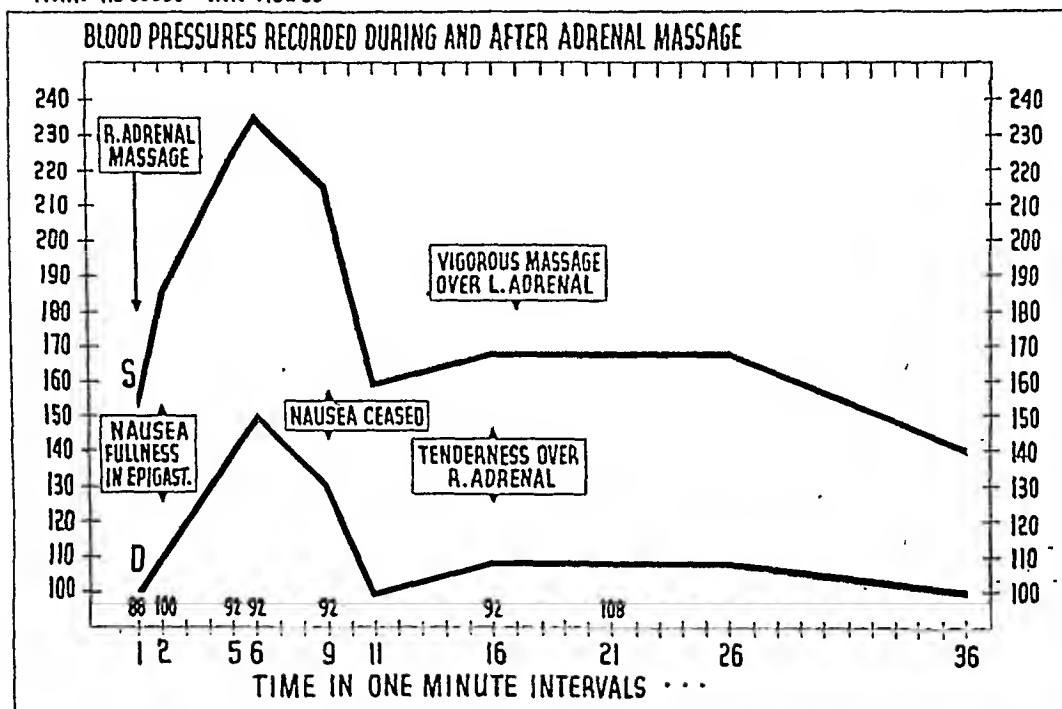


FIG. 4. Blood Pressures Recorded during and after Massage over Adrenal Areas.  
Time interval 1 minute.  
D = Diastolic blood pressure.  
S = Systolic blood pressure.

Before this procedure the blood pressure was 155 mm. Hg systolic and 100 mm. diastolic (pulse 88) and immediately afterwards the blood pressure was 185 mm. Hg systolic and 110 mm. diastolic (pulse 100) continuing to rise until it reached a peak of 235 mm. Hg systolic and 150 mm. diastolic in five minutes.

After the massage over the mass, the patient calmly complained of being sick at her stomach and then experienced sensations identical with the spontaneous attacks. The patient also complained of tenderness in the upper right quadrant.

When the base-line pressure was obtained (16 min.) the identical area in the left upper quadrant was manipulated in the same manner without any change in the blood pressure.

*Sweating Test* (Figure 5). Figure 5 outlines the areas of perspiration (in their relative amounts and location). The areas were of interest because before fluctuations

in blood pressure were recognized the possibility of some sympathetic nervous system involvement such as caused by mediastinal tumors had to be ruled out.

The test of sweating areas and outline of these areas were done by Minor's method.<sup>12</sup>

Minor's test, in short, gave us the outline of the sweating areas which were bilaterally symmetrical and most noticeable in the fold areas.

*Surgery* (Figure 6). After the diagnosis was established and the necessary clinical laboratory studies were complete, pre-operative preparation was begun. The patient received one-half grain phenobarbital every four hours for four days prior to the day of operation. This proved sufficient to prevent any severe spontaneous at-

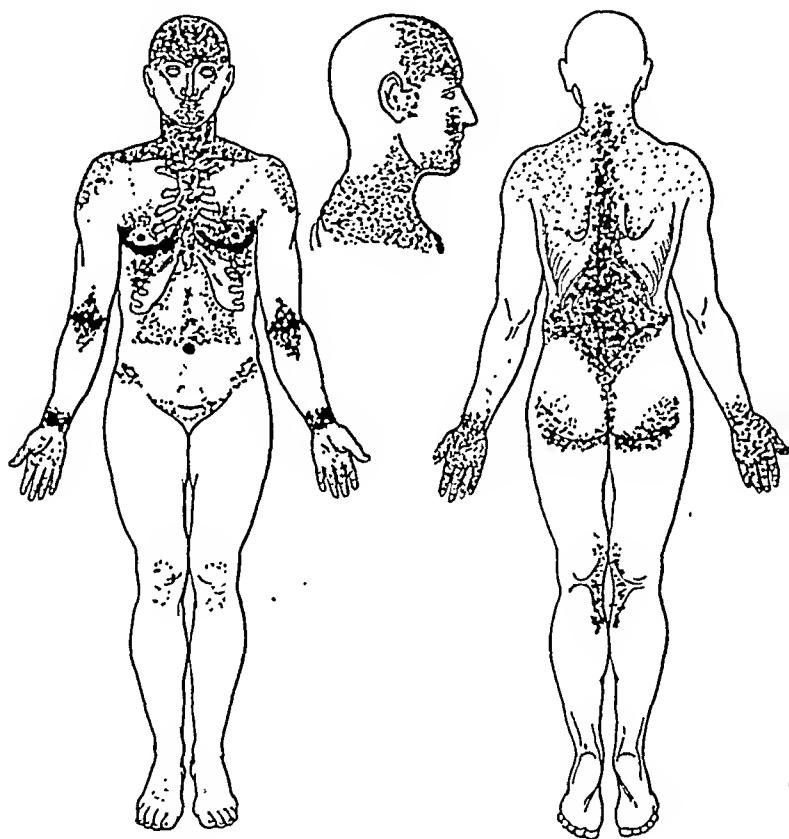


FIG. 5. Sweating Test, Minor's Method.

tack due to emotional upset. Two days before operation the patient was given hourly 15 gr. doses of sodium chloride in view of the post-operative adrenal cortical insufficiency which might have resulted.

Adequate preparation was made for any emergency which might have arisen during the surgical removal of the tumor. A vein was cannulated and a very slow drip rate established in order that drugs might be administered instantaneously if necessary.

The patient had gr. 1/150 atropine sulfate and avertin as pre-general anesthetic medication in her room. She was asleep when taken to the operating room. Her blood pressure was 140 mm. Hg systolic and 95 mm. diastolic. Nitrous oxide-ether anesthesia was then begun. Preoperative diagnosis was: Pheochromiocyoma of the right adrenal gland.

At no time during the operation for removal of the tumor did the blood pressure

approach the height reached during some of the spontaneous attacks—the peak being 225 mm. Hg systolic and 130 mm. diastolic.

**Incision:** High right rectus. Peritoneum and transverse aponeurosis muscle opened diagonally from upper portion of wound downward and outward. The blood pressure began to take a gradual upward swing at this point.

**Exploration:** Numerous band-like adhesions connected the upper surface of the liver with the under surface of the diaphragm. These had to be freed. Blood pressure readings had by this time leveled off to 220 mm. Hg systolic and 145 mm. diastolic. Palpation of the tumor over the right adrenal area was then accomplished by the operator. Palpation of it was very gentle but immediately caused slight rise in blood

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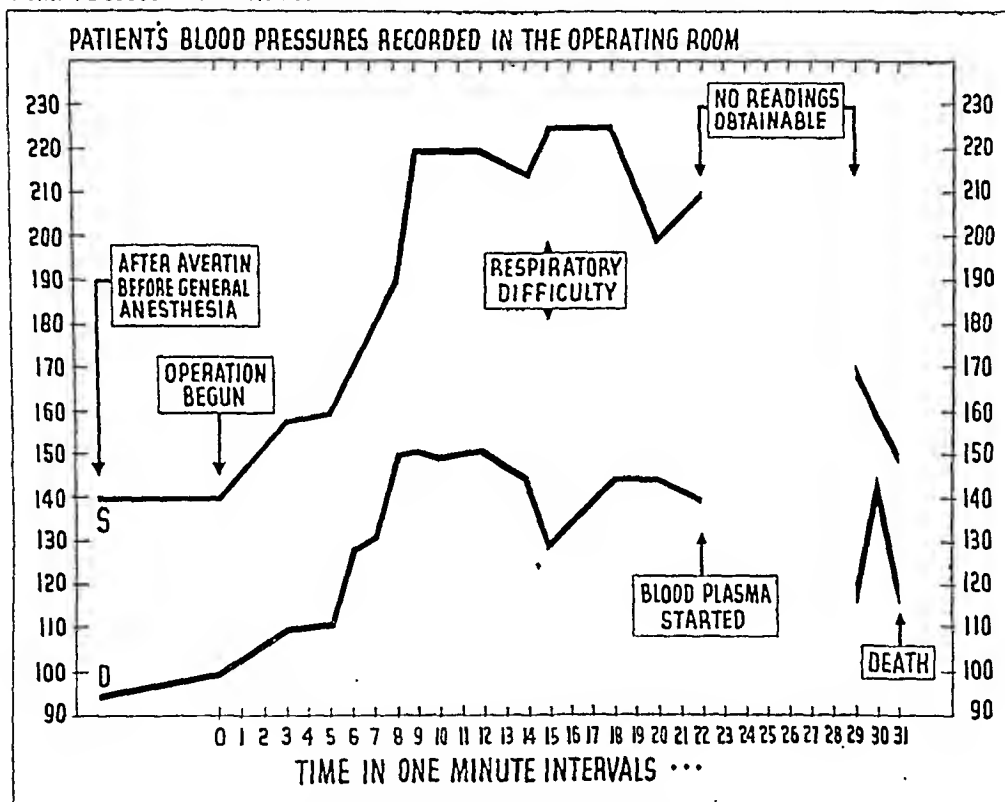


FIG. 6. Blood Pressure during Operation for Removal of the Tumor.

S = Systolic blood pressure.

D = Diastolic blood pressure.

pressure and respiratory difficulty. The operation was then discontinued for a time. The blood pressure came down and the condition of the patient seemed good. The liver was now retracted to the left and an attempt was made to separate the peritoneum along the line where it passed from the tumor to the under surface of the diaphragm. At this point the patient collapsed. During the collapse the wound was rapidly closed. The patient's condition and the size and location of the tumor warranted discontinuance of the operation and plans for a different approach after recovery. Her color was an ashen gray and great quantities of clear fluid poured from her nose and mouth. Although no blood pressure, pulse, or respirations were obtainable for a period of seven minutes, readings were again obtained and the blood pressure was 170 mm. Hg systolic

and 110 mm. diastolic . . . it began to fall again gradually and after four minutes the patient died despite every effort to save her.

Permission was obtained to remove the tumor. This was done through the original incision with most surprising ease. It was about the size of a medium orange, completely encapsulated, and seemed to have very few blood vessels attached to it.

The entire tumor weighed 350 grans. Part of the tumor was removed for microscopic study. The remainder was immediately packed in ice and sent to Dr.

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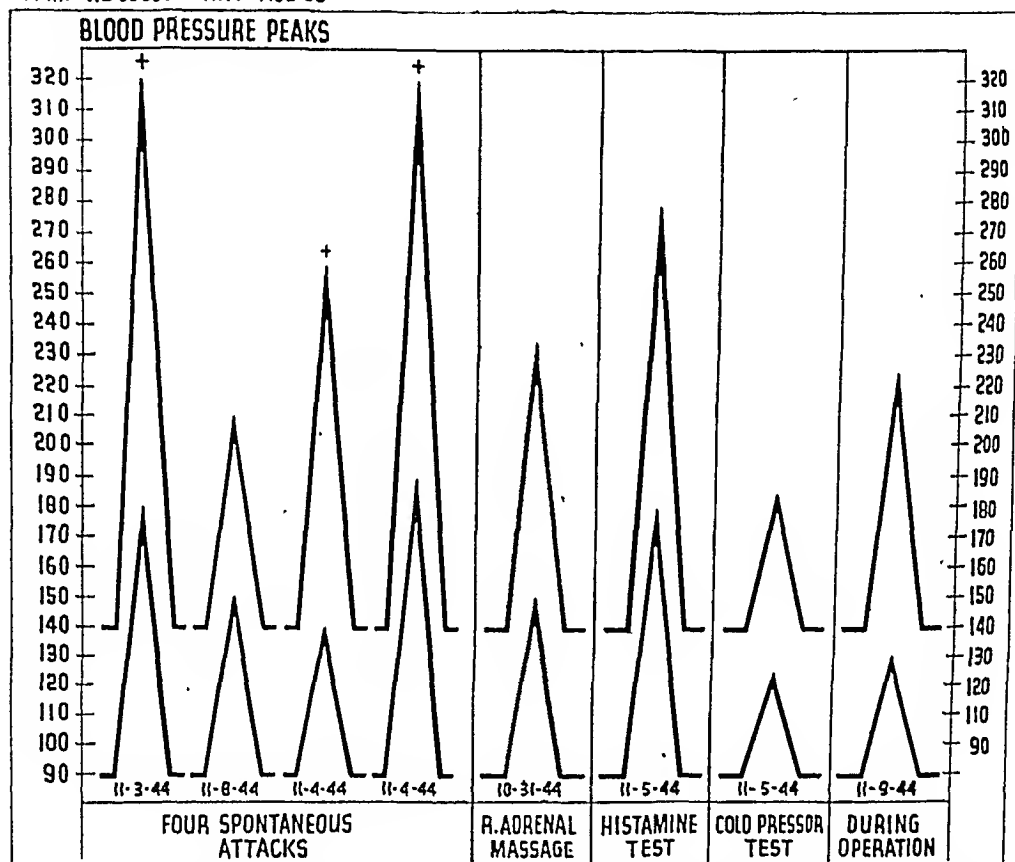


FIG. 7. Composite picture—blood pressure during various procedures. Four spontaneous attacks, the most severe of which resulted in a recordable blood pressure of 320 mm. Hg systolic and 180 mm. diastolic. Normal average base-line 140 mm. Hg systolic and 90 mm. diastolic. Right adrenal massage, 235 mm. Hg systolic and 145 mm. diastolic. The histamine test resulted in a peak pressure of 275 mm. Hg systolic and 175 mm. diastolic, but this attack was aborted by the use of nitroglycerine. The blood pressure rose to 185 mm. Hg systolic and 120 mm. diastolic during the "cold-pressor test."

K. K. Chen (Lilly Research Laboratory, Indianapolis, Indiana) who made an extract of the remaining 286 grams. This was made according to the method of Folin, Cannon, and Denis (Jr. Biol. Chem., 1912-13, xiii, 477), and a total volume of 12 liters was obtained (figure 8).

By a colorimetric comparison with a standard adrenalin solution, it was shown that the extract was 1.43 times as strong as a 1:10,000 adrenalin solution, volume for volume. The extract was then assayed by the blood pressure method of Elliott (Jr. Physiol., 1912, xlv, 374). It was shown that the extract by this procedure was 1.6

times as potent as a 1:10,000 adrenalin solution. An example of such a test is shown above. When calculated on the basis of the blood pressure method, the total amount of adrenalin present in 286 grams would be 1.92 grams, or 671 mg./100 gm. of the tumor.

Calculating then from the total weight, the amount of adrenalin in the whole tumor would then be 2.3496 grams. If we further calculate that a pair of beef adrenals, assayed biologically (Folin, Cannon, and Denis, Jr. Biol. Chem., 1912-13,

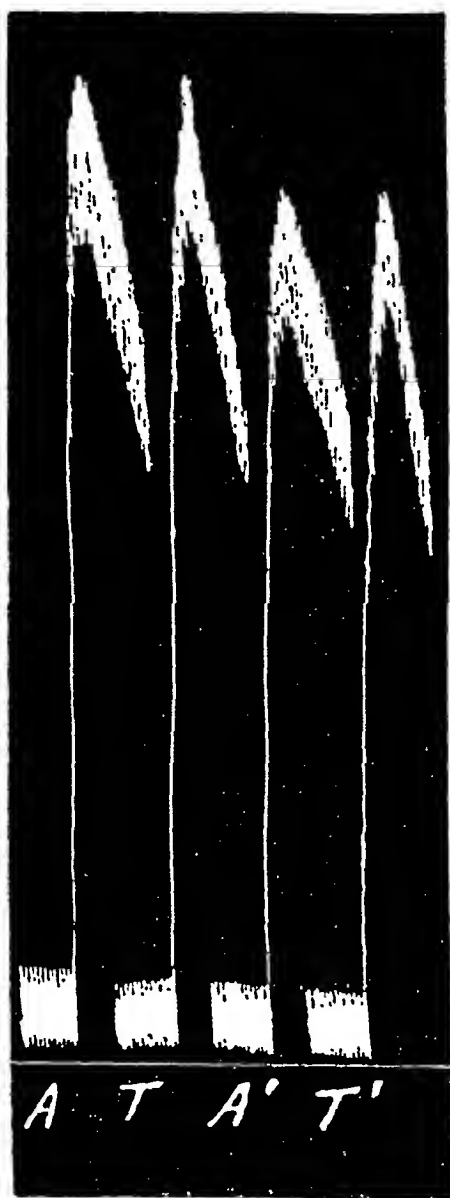


FIG. 8. Assay of the Adrenalin Content by the Blood Pressure Method

Dog, male, weighing 8.6 kg., was decerebrated and pithed—under artificial respiration. Both vagi were cut. The blood pressure responses were caused by the following solutions intravenously injected:

A—Adrenalin Solution, 1:10,000, 0.2 c.c.

T—Tumor Extract, 0.125 c.c.

A'—Adrenalin Solution, 1:10,000, 0.16 c.c.

T'—Tumor Extract, 0.10 c.c.

xiii, 477), contains 75 mg. of adrenalin, it will then take a herd of 31 cattle to give rise to the same amount of adrenalin that was present in this tumor.

Since an adult man has a maximum of 1 mg. of adrenalin in his adrenal glands (Elliott, *Proc., Jr. Physiol.*, 1913, xlv, xv), it would then take a company of 261 human subjects to give up the same amount of adrenalin as in our specimen.

Many of the tumors are cystic in nature and assay of a small piece of such a tumor would give misleading information as to the total amount of adrenalin in the tissue. We believe that the tumor is one of the very few that was assayed in its entirety, i.e., with exception of the small portion removed for pathological study and tissue section.

#### RÉSUMÉ OF POSTMORTEM DATA

(From protocol prepared by Department of Pathology) by Dr. F. Forry and Dr. A. Michael

There was a bilateral cervical lymphadenopathy. An easily palpable firm node was found some 3 cm. below the mastoid process on the right. The lung showed the features of a typical pulmonary edema. The paratracheal nodes were moderately enlarged. Examination of the tissues along each of the carotid sheaths revealed several normal appearing lymph nodes. No structures were identified grossly or histologically as carotid bodies. The left lobe of the thyroid measured 2 by 1½ by 2 cm. and was rather firmly attached to the surrounding tissue. Attached to the capsule were two small nodules grossly resembling parathyroid. These measured 2 by 3 by 4 mm. Microscopic sections of thyroid show normal appearing thyroid tissue within which lies a partially encapsulated area of neoplastic tissue. The neoplastic tissue appears in alveolar masses or small clumps of cells surrounded by a dense fibrous connective tissue stroma. The neoplastic cells are epithelial in type. They varied from 12 to 18 micra in diameter. The nuclei tend towards pyknosis. In some fields the stroma exceeds the neoplastic tissue. Strands of neoplastic cells are seen growing in lymphatic channels. Several of the lymph nodes of the cervical and paratracheal chains show masses of neoplastic tissue, morphologically the same as that in the thyroid.

The dorsal aorta showed very mild arteriosclerosis. Search was made for the aortic body but this was not identified grossly or microscopically.

Examination of the loose tissues about the site of the tumor of the right adrenal revealed no evidence of infiltration by neoplastic tissue. The stump of the right suprarenal vein was normal grossly and histologically. The left suprarenal weighed 13.5 grams. It contained two spherical nodules apparently developing in the medulla. Each was about a centimeter in diameter. The left suprarenal vein showed no evidence of invasion by neoplastic tissue.

The remaining gross findings have no significant bearing in this case.

The outstanding and striking clinical manifestations recorded in the clinical notes were shown to be due to a large pheochromocytoma originating in the right suprarenal gland.

Several microscopic sections of the adipose and connective tissues about the right suprarenal tumor and of tissues at its hilus showed no evidence of extension of neoplastic cells beyond the confines of the tumor (figure 9).

Microscopic study of the two 1 cm. nodules present in the left suprarenal shows the histological picture characteristic for pheochromocytoma. In sections fixed in Zenker's solution, some of the cells in each of these two tumors are seen to contain fine yellowish brown granules. Repeated transverse sections through the left suprarenal and its two neoplastic nodules and its hilus likewise did not reveal histologic

evidence of extension into blood channels, along lymphatics, or into connective tissues. Although the contact zone between each of the neoplastic nodules and surrounding suprarenal tissue was irregular, none of the sections showed tumor cells wandering away from the parent tumor mass. Demonstration of a positive "chromaffin reaction" leads to the conclusion that these masses are pheochromocytomas of independent or multi-centric origin. No lymph node neoplastic disease was found below the diaphragm or lower mediastinum. The lymph nodes affected by neoplastic disease were all situated in the right and left anterior cervical chain and paratracheal nodes. These contained masses of neoplastic epithelium histologically like that found in the left

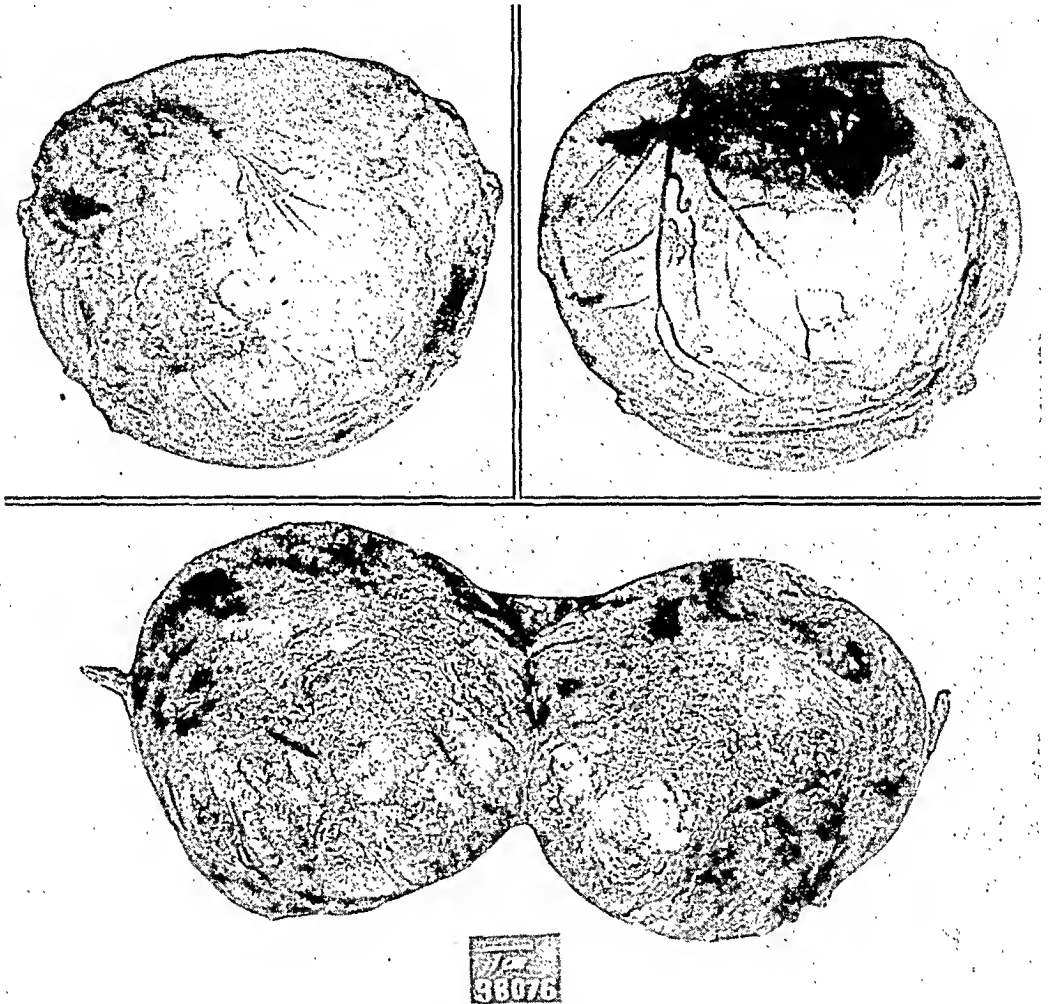


FIG. 9. Adrenal Tumor. Pheochromocytoma weighing 350 gm. and containing 2349 mg. epinephrine.

lobe of the thyroid. Sections through these nodes, the thyroid and adjacent tissue revealed numerous instances of lymphatic permeation. The neoplastic tissue in these nodes is histologically identical with that found in the thyroid. It does not resemble the tissue of the suprarenal neoplasms.

Anatomical Diagnoses: pheochromocytoma, right suprarenal; pheochromocytomas, left suprarenal; carcinoma, left lobe of thyroid; metastatic carcinoma (from thyroid) in cervical and paratracheal lymph nodes; pulmonary congestion and edema, bilateral.



Tissue sections made from the thyroid gland removed in a Des Moines hospital in 1938, were obtained recently. They show histological features identical with those of the neoplastic tissue found in the remaining thyroid tissue.

### SUMMARY AND CONCLUSIONS

The above represents a case report of pheochromocytoma, classical in all respects. In addition, there were the two tumors of like histological structure in the opposite adrenal. There was present an unrelated neoplasm, carcinoma of the thyroid with metastases to a cervical and the mediastinal lymph nodes. Of interest was the patient's tendency to center her discomfort during a paroxysm about the cervical node.

The patient uniformly showed the results anticipated in the various physiological tests. The histamine test as suggested by Roth and Kvale was, as clear cut in our case as in those described by them. As was shown by them further, the histamine test was quantitatively more excitatory than was the cold pressor test producing a rise in blood pressure of approximately 100 mm. after the latter test.

As is true in other cases reported, ours had hemithyroidectomy for relief of symptoms. This was in a way effective subjectively for four years, though it was obvious that the patient was not well. The extreme lability of such a patient in a surgical procedure is well exemplified. Although the picture is quite classical and clear in most cases and a few simple observations will usually suffice to establish a diagnosis, yet a number of available tests more accurately demonstrate the physiological processes. For example, the basal metabolic rate was high, the glucose tolerance curve was of the diabetic type, the cholesterol high, roentgen-ray examination revealed depression of the kidney calices, the cold pressor test showed a marked response and massage over the tumor gave rise to a typical paroxysm as did the histamine test.

Complete detailed laboratory, clinical, physiological and pathological studies are included in the above report.

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## EDITORIAL

### *PENICILLIN IN THE TREATMENT OF SYPHILIS*

LIKE many another new form of therapy, the penicillin treatment of syphilis has progressed through the cycle of dubiety, enthusiasm and reaction. Mahoney's original report<sup>1</sup> that penicillin is effectual against *T. pallidum* was received with some caution, but as laboratory and clinical confirmation of this observation rapidly became available, reserve quickly gave way to enthusiasm. So promising did this new form of therapy appear that in September 1943, within three months of the first public announcement, a nationwide co-operative study was organized under the auspices of the Committee on Medical Research. In less than a year penicillin was adopted for routine use in early syphilis by the United States Army. Since then the limitations of this form of therapy gradually have become apparent.

Even the most skeptical observer no longer denies that penicillin is a valuable adjunct to syphilotherapy, nor that it is, in some respects, superior to any previous form of treatment. That it has serious drawbacks is recognized by its most ardent protagonists.

The principal advantages of penicillin in the treatment of syphilis are its lack of toxicity, and the fact that the therapeutic schedule need not be inordinately prolonged. Consequently, the full course of treatment is almost invariably completed. This is not the case with any form of arsenotherapy, where toxic reactions increase in frequency the more the total duration of treatment is compressed, and where case-holding becomes increasingly difficult as the time period of therapy is prolonged.

The principal disadvantages of penicillin therapy are the probable essentiality of hospitalization, when the drug is given in aqueous solution, and the significant number of treatment failures (relapse and seroresistance in early syphilis, submaximal improvement in certain forms of late syphilis).

In early syphilis, the results of penicillin therapy are conditioned largely by two factors: (1) the duration of the disease; and (2) the time-dose relationships of penicillin administration.

As with all other forms of therapy, the earlier in the course of syphilitic infection penicillin treatment is begun, the better are the results. In the Army,<sup>2</sup> the failure rate in secondary syphilis was more than four times that of patients treated in the primary stage of the disease.

There is ample evidence, both from the clinic<sup>3</sup> and from the laboratory<sup>4</sup>

<sup>1</sup> MAHONEY, J. F., ARNOLD, R. C., and HARRIS, A.: Penicillin treatment of early syphilis: preliminary report, *Ven. Dis. Inform.*, 1943, xxiv, 355.

<sup>2</sup> News and Comments: Status of penicillin treatment of early syphilis, *Bull. U. S. Army Med. Dept.*, 1946, v, 1.

<sup>3</sup> McDERMOTT, W., BENOIT, M., and DuBOIS, R.: Time-dose relationships of penicillin therapy: regimens used in early syphilis, *Am. Jr. Syph., Gonor. and Ven. Dis.*, 1945, xxix, 345.

<sup>4</sup> EAGLE, H., MAGNUSON, H. J., and FLEISCHMAN, R.: The effect of the method of administration on the therapeutic efficacy of sodium penicillin in experimental syphilis, *Bull. Johns Hopkins Hosp.*, 1946, lxxix, 168.

that the therapeutic effectiveness of penicillin is profoundly influenced by the time-dose relationships of its administration. Penicillin, unlike arsenic, is not bound by spirochetal organisms and its activity appears to depend upon the length of time during which therapeutically effective levels are available at the site of action. Precisely what the minimum effective level is and how long it must be maintained have not yet been determined. It is clear, however, that penicillin is actively treponemicidal in extremely low concentrations. It is also evident that relatively low concentrations acting over long periods of time are far more efficacious than high concentrations of brief duration. Increasing the tissue levels of penicillin, by giving higher dosages per injection does tend to increase its therapeutic effectiveness in the treatment of syphilis, at least up to a certain point. Of far greater importance, however, appears to be the time period over which *T. pallidum* is exposed to the action of the drug. Increased total doses of penicillin thus influence the results of therapy more if used to prolong the course of treatment than if given to augment the blood level at any one time.

The necessity of hospitalization for patients receiving penicillin as therapy for syphilis significantly reduces its general utility, for the number of hospital beds available for this purpose is limited, despite the Rapid Treatment Center program of the United States Public Health Service.

To be feasible as an agent for treatment of ambulatory syphilis patients in the clinic and in the physician's office, a modified penicillin with prolonged activity is desirable. Many attempts have been made to extend the duration of penicillin action, either by delaying its absorption or by blocking its renal tubular excretion, but by far the most satisfactory modification presently available is the suspension of penicillin in peanut oil and beeswax ("POB").<sup>5</sup>

"POB" has been used in the treatment of syphilis. Preliminary reports<sup>6,7</sup> suggest that the results may be sufficiently satisfactory to warrant more widespread application. Treatment schedules utilizing "POB," alone and in combination with mapharsen or bismuth are being evaluated currently by the clinics cooperating in the nationwide syphilis study. Already there is some indication that with as much as 9.6 million units of penicillin in oil and beeswax over a period of 16 days, there is a not inconsiderable number of treatment failures.

Indeed, with any schedule of penicillin administration the results of which are presently available, there has been a high incidence of treatment failures.<sup>8</sup> "Relapse" rates after the Army employed 2,400,000 units in seven and one-half days have been several times as high as those after any schedule

<sup>5</sup> ROMANSKY, M. J., and RITTMAN, G. E.: Method of prolonging action of penicillin, *Science*, 1944, c, 196.

<sup>6</sup> KOCH, R. A.: Ambulatory intensive treatment of syphilis with calcium penicillin in oil and wax, *Urol. and Cut. Rev.*, 1946, 1, 461.

<sup>7</sup> ROMANSKY, M. J., and REIN, C. R.: Treatment of early syphilis with calcium penicillin-oil-beeswax, Jr. *Am. Med. Assoc.*, 1946, cxxxii, 847.

<sup>8</sup> Committee on Medical Research and the United States Public Health Service: The treatment of early syphilis with penicillin, Jr. *Am. Med. Assoc.*, 1946, cxxxi, 265.

of arsenobismuth therapy, prolonged or intensive (provided that the latter were fully completed).

There is here involved the possibility that penicillin actually may be more efficacious in early syphilis than appears from this comparison, and that many so-called relapses actually represent reinfection.<sup>9</sup> Unfortunately, this point is incapable of determination on the basis of existing clinical and experimental data.

It is believed that this excessively high incidence of treatment failures from penicillin may be reduced in two ways. The total duration of therapy may be prolonged, in which case there arises the problem of case-holding, so frequently encountered during metal chemotherapy. Perhaps a more promising approach is the addition to the penicillin treatment scheme of concurrently administered metal chemotherapy.

Eagle and his co-workers<sup>10</sup> have demonstrated that when penicillin and oxophenarsine hydrochloride are administered concurrently to syphilitic rabbits, the therapeutic effects not only are additive but actually synergistic. This important laboratory observation has been studied by the clinics cooperating in the penicillin study, and the clinical results following the use of penicillin with an arsenoxide have proved superior to those with penicillin alone. Administered in combination with bismuth, the immediate clinical results also have been superior to those with penicillin alone.

It must be recognized, however, that the concurrent administration of arsenicals introduces a risk of serious reactions in direct proportion to the total amount of the drug given, and in inverse proportion to the time interval over which it is administered.

In view of this and other considerations, there is no unanimity of opinion as to the desirability of combining penicillin and oxophenarsine hydrochloride in the routine treatment of early syphilis. Some have expressed the belief that the results with penicillin alone, when administered in adequate amounts over a long enough period of time, are satisfactory in a sufficiently large proportion of patients to justify eliminating arsenicals from the original course of treatment, reserving their use for relapsing cases. Others believe that the additional therapeutic effectiveness provided by arsenic warrants the increased risk.

In the management of neurosyphilis, penicillin is proving of significant worth. Upon the cerebrospinal fluid abnormalities and especially upon the pleocytosis and elevated protein content, which have been considered an indication of the "activity" of the process in the central nervous system (Dattner-Thomas<sup>11</sup>), penicillin exerts a profoundly favorable effect. This is true

<sup>9</sup> Editorial: The changing concept of reinfection with syphilis and its applicability as a criterion of cure, *Am. Jr. Syph., Gonor. and Ven. Dis.*, 1945, xxix, 474.

<sup>10</sup> EAGLE, H., MAGNUSON, H. J., and FLEISCHMAN, R.: The synergistic action of penicillin and mapharsen (oxophenarsine hydrochloride) in the treatment of experimental syphilis, *Jr. Ven. Dis. Inform.*, 1946, xxvii, 3.

<sup>11</sup> DATTNER, B., THOMAS, E. W., and WEXLER, G.: The management of neurosyphilis, 1944, Grune and Stratton, New York.

not only in asymptomatic neurosyphilis,<sup>12</sup> but also in the various clinical syndromes of syphilis of the central nervous system,<sup>13</sup> although post-treatment "reactivation" has been noted somewhat more frequently among those with symptomatic (usually parenchymatous) neurosyphilis than among those with asymptomatic involvement of the neuraxis.

In asymptomatic neurosyphilis, where the only evidence of involvement of the central nervous system is an abnormal spinal fluid, the results of therapy can be adjudged only by the response of the spinal fluid and the incidence of progression to clinical neurosyphilis. The spinal fluid abnormalities in early and late asymptomatic neurosyphilis respond dramatically to penicillin. Improvement is manifest promptly on cell count and protein content, more gradually on the colloidal test, and last of all, on the Wassermann reaction. Spinal fluid normality, once achieved, seems usually to be stable. The rapidity with which the spinal fluid becomes normal following penicillin therapy is dependent upon the degree of the pre-treatment abnormalities and the duration of the syphilitic infection. Lesser degrees of abnormality and those occurring within the first two years of the disease disappear rapidly; those more extensive and of longer duration improve slowly over a period of years.

The ultimate result in terms of clinical progression will not be known for many years. If, however, the favorable spinal fluid responses thus far noted are sustained, the incidence of clinical neurosyphilis developing in this group of patients should be low.

The clinical manifestations of neurosyphilis are protean: some due to active inflammation, others to degenerative processes; some reversible, others the result of irreparable damage of neural tissues. In its effects upon these clinical manifestations, which include such widely dissimilar symptom complexes as acute syphilitic meningitis, general paresis, tabes dorsalis, and Erb's spastic paraplegia, the presently available information suggests that penicillin is superior to metal chemotherapy but that it gives little promise of clinical results in parenchymatous neurosyphilis superior to those obtainable with fever therapy.

It should be pointed out, however, that such improvement as does follow penicillin therapy is attained at no risk to the patient, and in a shorter time and with less inconvenience to him than attends either therapeutic fever or protracted metal chemotherapy.

In acute syphilitic meningitis, the results of therapy with penicillin used alone are excellent,<sup>14</sup> but in parenchymatous neurosyphilis, less outstandingly favorable. In at least one clinic which has used both penicillin alone and penicillin as an adjunct to malarial fever therapy, greater success in general

<sup>12</sup> MOORE, J. E., and MOHR, C. F.: Penicillin in the treatment of neurosyphilis. I. Asymptomatic neurosyphilis, *Am. Jr. Syph., Gonorr. and Ven. Dis.*, 1946, xxx, 405.

<sup>13</sup> REYNOLDS, F. W., MOHR, C. F., and MOORE, J. E.: Penicillin in the treatment of neurosyphilis. III. Changes in cerebrospinal fluid abnormalities, *Ann. Int. Med.* (In press.)

<sup>14</sup> NELSON, R. A., and MOORE, J. E.: Acute syphilitic meningitis treated with penicillin: a progress report, *Am. Jr. Syph., Gonorr. and Ven. Dis.*, 1946, xxx, 227.

paresis<sup>15</sup> and in tabes dorsalis<sup>16</sup> has been obtained with the combined therapy. There also are indications that penicillin alone may prove inferior to malaria plus penicillin in primary optic atrophy, late syphilitic nerve deafness, and Erb's spastic paraplegia.

For the present at least, there is reason to believe that the concurrent administration of penicillin with malarial fever therapy offers the patient with late parenchymatous neurosyphilis the greatest promise of a favorable outcome. It is probably the treatment of choice, therefore, in those forms of neurosyphilis which carry a serious risk to life or important bodily function: namely, paresis and taboparesis, primary optic atrophy and nerve deafness. In acute syphilitic meningitis, early or late asymptomatic neurosyphilis and in meningovascular neurosyphilis, therapy with penicillin alone may be given initially with good prospects of a favorable response.

The therapeutic problems in tabes dorsalis and in Erb's spastic paraplegia require further consideration. In each, the outlook ultimately is for distressingly chronic invalidism. Since, however, the evolution of these conditions is gradual, with no immediate threat to life or vital bodily function, and since these patients frequently are in such poor general physical condition as to be poor fever therapy risks, it is not unreasonable first to employ a form of therapy (e.g. penicillin) which is completely safe, provided there is any reasonable prospect that such therapy may be beneficial. In tabes dorsalis there is such a prospect, but in Erb's spastic paraplegia<sup>17</sup> there appears to be none.

Prior to the advent of penicillin, it was believed desirable to follow malaria therapy with a prolonged course of metal chemotherapy, not only to consolidate the effects of the fever but also to prevent progression of the disease in other organs, particularly in the cardiovascular system. The concomitant use of penicillin may well obviate the necessity for subsequent chemotherapy and thus significantly reduce the total duration of treatment.

Moreover, with penicillin, the advantages of fever therapy have been extended to that group of patients who are unsuitable for the rigorous full course of inoculation malaria. Rose and his co-workers<sup>18</sup> believe their results with an abbreviated course of malaria, given concomitantly with penicillin, were as satisfactory as those with a full course of malaria alone.

Gummatous lesions of the skin and bony skeleton,<sup>19</sup> and of such viscera as the liver<sup>20</sup> heal under therapy with penicillin. The healing process is no

<sup>15</sup> REYNOLDS, F. W., MOHR, C. F., and MOORE, J. E.: Penicillin in the treatment of neurosyphilis. II. Dementia paralytica, Jr. *Am. Med. Assoc.*, 1946, cxxxi, 1255.

<sup>16</sup> CHESNEY, L. P., and REYNOLDS, F. W.: Penicillin in the treatment of neurosyphilis. IV. Tabes dorsalis. To be published.

<sup>17</sup> TUCKER, H. A.: Penicillin treatment of Erb's syphilitic spinal spastic paraplegia, *Bull. Johns Hopkins Hosp.*, 1946, lxxviii, 161.

<sup>18</sup> ROSE, A. S., TREVETT, L. D., HINDLE, J. A., PROUT, C., and SOLOMON, H. C.: Penicillin treatment of neurosyphilis, *Am. Jr. Syph., Gonorr. and Ven. Dis.*, 1945, xxix, 487.

<sup>19</sup> DEXTER, D. D., and TUCKER, H. A.: Penicillin treatment of benign late gummatous syphilis: a report of twenty-one cases, *Am. Jr. Syph., Gonorr. and Ven. Dis.*, 1946, xxx, 211.

<sup>20</sup> TUCKER, H. A., and DEXTER, D. D.: Treatment of gummatous hepatic syphilis with penicillin: Report of two cases, *Arch. Int. Med.*, 1946, lxxviii, 313.

more rapid than with metal chemotherapy. Inflammatory ocular lesions respond quickly, excepting interstitial keratitis where the results are no better than with older forms of therapy.

In cardiovascular syphilis and in late latent syphilis, the evaluation of the usefulness of any therapeutic agent involves many years of post-treatment observation. There is, as yet, therefore, no information as to the results of penicillin therapy in these conditions. Caution has been urged in the use of large initial doses of penicillin in the presence of overt cardiovascular syphilis, in view of the possible complications from therapeutic shock.

It is obvious, however, that treatment with penicillin offers nothing to those with late latent syphilis whose serologic tests remain positive following prolonged chemotherapy. To subject these patients to further therapy of any kind, solely for the purpose of attaining seronegativity, is to kindle false hopes and to waste time, money and effort.

In the prevention of prenatal infection through treatment of pregnant women with syphilis, penicillin has been highly efficacious. Here it probably is, as Goodwin and Moore<sup>21</sup> suggest, the present therapy of choice. Penicillin readily passes the placental barrier and its treponemicidal action is available to the fetus in utero. It appears, despite the contentions of some, not to provoke uterine contractions and not to precipitate premature labor. The outlook for a nonsyphilitic child following penicillin therapy is excellent. Even among those mothers whose syphilitic infection has been recently acquired and in whom the risk to the child is great, there have been remarkably few treatment failures.

Those treating patients with syphilis have in penicillin a drug of negligible toxicity, readily administered, but with definite limitations in therapeutic effectiveness. It is far from being the ideal form of treatment. Yet it has, for the present at least, a place in the treatment of syphilis as the most desirable form of therapy presently available for certain of the protean manifestations of this disease, and as an adjunct to older methods in others.

F. W. R.

<sup>21</sup> GOODWIN, M. S., and MOORE, J. E.: Penicillin in prevention of prenatal syphilis, *Jr. Am. Med. Assoc.*, 1946, cxxx, 688.



## REVIEWS

*Carbohydrate Metabolism.* By SAMUEL SOSKIN, M.D., Director of the Research Institute, Michael Reese Hospital; Medical Director, Michael Reese Hospital; and Professorial Lecturer in Physiology, University of Chicago; and RACHMIEL LEVINE, M.D., Director of Metabolic Research and Endocrine Research, Michael Reese Hospital. 315 pages; 25 × 17.5 cm. 1946. University of Chicago Press, Chicago, Ill. Price, \$6.00.

This volume fills a need for a comprehensive review of carbohydrate metabolism. It was written to serve as a text for students in biochemistry, physiology, and medicine but it should prove valuable to anyone interested in any phase of metabolism. The authors have presented their subject from a broad point of view and have therefore included various aspects of protein and fat metabolism, pointing out the artificial barriers which have separated the teaching of these subjects in the past.

The volume is divided into five main sections: the biochemistry and energetics, introductory physiological considerations, critical survey of the classical criteria of diabetes, the rôle of the endocrine glands in carbohydrate metabolism, and integration of physiological and clinical aspects. Numerous tables, illustrations and diagrams are helpful in following the complex relationships of various factors which influence the metabolic processes. The selected bibliography contains over 1200 references to original sources of significant experimental facts, to useful reviews, and to discussions of topics which could not be included in this volume.

The authors have drawn freely on the results of their own research in carbohydrate metabolism and have stressed the overproduction theory of diabetes. Whether or not one agrees entirely with their conclusions on the mechanism of the high blood sugar in diabetes mellitus, one is impressed with the extensive studies on carbohydrate utilization in the intact and the eviscerated animal which they have carried out during the past few years. One feels, however, that some of the fundamental studies on enzymes and enzyme systems could have been presented in a little greater detail. It is regrettable that the epoch-making discovery of Cori and his associates that insulin counteracts the inhibition of hexosekinase by one of the anterior pituitary hormones is not fully discussed.

This volume should prove extremely useful to anyone interested in metabolism as it coördinates a great deal of material which is not otherwise readily available.

M. A. A.

*Currents in Biochemical Research.* Edited by DAVID E. GREEN. 486 pages; 24 × 16.5 cm. 1946. Interscience Publishers, Inc., New York. Price, \$5.00.

"Currents in Biochemical Research" consists of 31 essays on various biochemical topics written by authorities in their respective fields. Their aim has been to strip their presentations of highly technical terminology without sacrificing accuracy so that workers in related fields may follow the progress made and recognize the unsolved problems in biochemistry outside their own specialty. The essays are not intended to be extensive reviews but rather to point out the highlights in recent work. The papers are on a wide variety of subjects, biochemical problems related to pharmacology, chemotherapy, public health and genetics on the one hand and organic and physical chemistry applied to biochemical research on the other. One is impressed that in seemingly widely divergent topics, enzymes and enzyme systems are coming to be a common meeting ground for biochemists.

A number of chapters should be of interest to those in medical fields. These include short discussions by Dr. C. H. Best on insulin and diabetes, histamine and histaminase, heparin, lipotropic factors, and war medical research. The mucolytic enzymes, lysozyme and hyaluronidase are discussed in one paper and their possible

relationship to streptococcus infections and rheumatic fever is pointed out. Dr. C. L. Hoagland has written on "Biochemical Problems Posed by Diseases of the Muscle." With the constant broadening of scientific horizons one appreciates a volume of this type which presents authoritative information on many topics.

M. A. A.

### BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Endocrine Function of the Hypophysis.* By HARRY B. FRIEDGOOD, M.D. 828 pages; 24 × 16 cm. 1946. Oxford University Press, New York. Price, \$4.50.

*The Chest. A Handbook of Roentgen Diagnosis.* By LEO G. RIGLER, M.D. 352 pages; 21 × 14.5 cm. 1946. Year Book Publishers, Chicago. Price, \$6.50.

*Ulcer of the Stomach, Duodenum and Jejunum.* By RALPH C. BROWN, M.D. 172 pages; 24 × 16 cm. 1946. Oxford University Press, New York. Price, \$2.25.

*Modern Development of Chemotherapy.* By E. HAVINGA, H. W. JULIUS, H. VELDSTRA and K. C. WINKLER. 175 pages; 21 × 15 cm. 1946. Elsevier Publishing Company, Inc., New York-Amsterdam. Price, \$4.00.

*Medical Research. A Symposium.* Edited by AUSTIN SMITH, M.D. 169 pages; 24 × 16 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, \$5.00.

*Intracranial Complications of Ear, Nose and Throat Infections.* By HANS BRUNNER, M.D., University of Illinois. 444 pages; 23.5 × 15.5 cm. 1946. Year Book Publishers, Inc., Chicago. Price, \$6.75.

*The Differential Diagnosis of Jaundice.* By LEON SCHIFF, Ph.D., M.D. 313 pages; 21 × 14.5 cm. 1946. Year Book Publishers, Chicago. Price, \$5.50.

*Introduction to Surgery.* By VIRGINIA KNEELAND FRANTZ, M.D., and HAROLD DORTCH HARVEY, M.D. 216 pages; 19 × 12.5 cm. 1946. Oxford University Press, New York. Price, \$2.50.

*Eye Manifestations of Internal Diseases.* Second Edition. By I. S. TASSMAN, M.D., University of Pennsylvania. 613 pages; 25 × 17 cm. 1946. The C. V. Mosby Company, St. Louis. Price, \$10.00.

*Some Chapters in Cambridge Medical History.* Sir WALTER LANGDON-BROWN, Emeritus Professor of Physic in the University of Cambridge. 119 pages; 19.5 × 13 cm. 1946. Cambridge; at the University Press, New York, The Macmillan Company. Price, \$1.75.

*La Preparacion de Soluciones "Tipo"—Para el Analisis Volumetrico.* By WALTER JUNG and CARLOS E. CARDINI. 90 pages; 24 × 17 cm. 1946. Biblioteca Central de la Universidad Nacional de Tucuman, Tucuman-R. Argentina.

*Menstrual Disorders and Sterility.* Second Edition. By CHARLES MAZER and S. LEON ISRAEL. 570 pages; 24 × 16.5 cm. 1946. Paul B. Hoeber, Inc., New York. Price, \$7.50.

*Cor Pulmonale.* By J. CODINA-ALTES, M.D. 205 pages; 23.5 × 17 cm. 1944. Libreria Editorial, Cientifico Medica Espanola, Madrid.

# COLLEGE NEWS NOTES

## LIFE MEMBERS

The College is gratified to announce that the following Fellows, listed in order of their subscription, have become life members of the College:

Dr. Andrew C. Blair, F.A.C.P., Charlotte, N. C., November 18, 1946  
Dr. Paul F. Liva, F.A.C.P., Lyndhurst, N. J., November 21, 1946  
Dr. J. K. Williams Wood, F.A.C.P., Troy, Pa., November 25, 1946  
Dr. C. DeWitt Briscoe, F.A.C.P., Panama, R. P., December 5, 1946  
Dr. Carrol C. Turner, F.A.C.P., Memphis, Tenn., December 5, 1946  
Dr. J. Russell Twiss, F.A.C.P., New York, N. Y., December 13, 1946  
Dr. William R. Blue, F.A.C.P., Memphis, Tenn., December 16, 1946  
Dr. William M. Sheppe, F.A.C.P., Wheeling, W. Va., December 16, 1946  
Dr. Hildegard G. Sinnock, F.A.C.P., Quincy, Ill., December 16, 1946

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## A.C.P. DUES RESTORED TO FORMER RATE

Prior to 1933, College dues were \$20.00 per annum for Fellows and \$15.00 for Associates (\$10.00 in case of full-time teachers, military officers, research workers, et al.). On January 1 of that year, due to the depression, the dues were reduced to \$15.00 and \$12.00 respectively (the minimum \$10.00 dues continuing to apply in case of full-time teachers, etc.).

On October 20, 1946, the Board of Regents voted unanimously to restore the dues to the former rates. Everything costs materially more now; College services and activities have been tremendously increased; the journal costs at least 35 per cent more to publish; the College cannot continue its broad program or plan desired expansions without increased dues.

The Action by the Board of Regents was taken after careful study and analysis. The College dues are considerably less than those of most other national medical societies. Even in some state medical societies, the dues are as high as \$50.00 per annum (in one state society, \$100.00).

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The Annual Regional Dinner Meeting of the College, Southern California Chapter, will be held on February 7 at the Alexandria Hotel, Los Angeles, under the direction of Dr. Leland Hawkins, A.C.P., Governor for the district.

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## HOTEL RESERVATIONS—CHICAGO ANNUAL SESSION

The American College of Physicians has been guaranteed adequate hotel accommodations for all the physicians who desire to attend its Annual Session at Chicago, April 28 to May 2, inclusive, 1947, but the Chicago Convention Bureau and the Chicago hotels have requested the College to clear all reservations through a Housing Committee.

Hotels with which official arrangements have been made, and all of which are in fairly close proximity to the headquarters hotel, the Palmer House, include the Stevens, Morrison, Congress, Sherman, Chicagoan and Bismarck. All reservations at these hotels must be cleared through the Housing Committee. Those desiring to stay at other hotels in Chicago may arrange their reservations personally and directly.

All hotel applications received up to January 1, 1947, were handled by the Executive Office of the College; all applications thereafter are referred to the Housing Committee. The form suggested for application is as follows:

## HOUSING COMMITTEE

AMERICAN COLLEGE OF PHYSICIANS

The Chicago Convention Bureau

33 N. LaSalle St.

Chicago 2, Ill.

Hotel Reservations for the period of the American College of Physicians Annual Session, Chicago, April 28-May 2, are requested as follows:

Hotel preferred: \_\_\_\_\_; 2nd choice: \_\_\_\_\_

Type of room: ( ) Single; ( ) Double; ( ) Double, twin beds;  
( ) Suite, twin bedded room and parlor.

Price range per day: \$\_\_\_\_\_ to \$\_\_\_\_\_

Date of arrival: \_\_\_\_\_; date of departure \_\_\_\_\_

Name and address:

*Single Rooms:* Very few single rooms are available. Attendants are urged to share twin bedded rooms with acquaintances or friends. The Housing Committee has only 350 single rooms at its disposal.

*The Palmer House,* as official headquarters, will house all Officers, Regents and Governors of the College, Speakers on the program and Distinguished Guests. These reservations will be handled personally by the Executive Secretary of the College, and applications from this group should be submitted only to the Executive Secretary.

*Technical Exhibitors:* The Technical Exhibitors will be housed at the Congress Hotel as their official headquarters. Exhibitors may apply directly to Mr. Daniel Amico, Sales Manager of the Congress Hotel, identifying themselves with the meeting of the American College of Physicians.

Applications for hotel accommodations to the Housing Committee will be promptly acknowledged; the Committee will clear all applications once weekly with the Convention Bureau; each hotel will be requested to confirm reservations assigned to it.

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### INDEX AND SUMMARY OF REGISTRATIONS, AUTUMN COURSES, 1946

No.	Title	Institution	Director	Dates
1.	Internal Medicine	University of Pittsburgh School of Medicine, Pittsburgh, Pa.	Dr. R. R. Snowden	September 2-14
2.	Psychosomatic Medicine	University of Colorado School of Medicine and Hospitals, Denver, Colo.	Dr. Franklin G. Ehaugh	September 23-28
3.	Internal Medicine	University of Oregon Medical School, Portland, Ore.	Dr. Homer P. Rush	October 7-19
4.	Clinical Neurology	Jefferson Medical College, Philadelphia, Pa.	Dr. Bernard J. Alpers	October 14-18
5.	Clinical Medicine from the Hematologic Viewpoint	Ohio State University College of Medicine, Columbus, Ohio	Dr. Charles A. Doan	October 21-26
6.	Internal Medicine	Gallinger Municipal Hospital, Washington, D. C.	Dr. Wallace M. Yater	Oct. 21-Nov. 1
7.	Allergy	Roosevelt Hospital, New York, N. Y.	Dr. Robert A. Cooke	November 4-9
8.	Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease	Massachusetts General Hospital, Boston, Mass.	Dr. Paul D. White	November 4-9
9.	Gastro-enterology	University of Chicago School of Medicine, Chicago, Ill.	Dr. Walter L. Palmer	November 11-16

No.	Title	Institution	Director	Dates
10.	Selected Problems in Internal Medicine	Western Reserve University and Affiliated Hospitals, Cleveland, Ohio	Dr. Joseph M. Hayman, Jr.	November 18-23
11.	Internal Medicine	McGill University and Royal Victoria Hospital, Montreal, Que.	Dr. J. C. Meakins	Nov. 25-Dec. 6
12.	Bacterial Chemotherapy	Washington University School of Medicine, St. Louis, Mo.	Dr. W. Barry Wood, Jr.	December 2-7
13.	Cardiology	University of Michigan Medical School, Ann Arbor, Mich.	Dr. Frank N. Wilson	December 2-7

No.	Fellows	Associates	Non-members	TOTAL
1.	6	5	15	26
2.	13	4	2	19
3.	4	6	4	14
4.	25	11	12	48
5.	36	19	20	75
6.	20	12	24	56
7.	11	5	9	25
8.	56	19	0	75
9.	20	21	26	67
10.	5	13	12	30
11.	20	7	8	35
12.	10	3	1	14
13.	31	9	0	40
	<hr/> 257	<hr/> 134	<hr/> 133	<hr/> 524

During the Spring, 1946, the College conducted ten courses, with a registration of 334 Fellows, 151 Associates and 199 Non-Members; Total, 684.

Summary of Registrations for the Year, 1946:

591 Fellows

285 Associates

876 A.C.P. Members

332 Non-Members

1,208 Grand Total

#### POSTGRADUATE COURSES, SPRING 1947

The detailed Postgraduate Bulletin, Spring, 1947, is now available, and copies have been mailed to all members of the College and to non-members who have had their names placed on the Mailing List.

Fees for all courses, except No. 1, are \$20.00 per week for A.C.P. Members; \$40.00, for Non-Members. Fee for Course No. 1, \$40.00 for Members; \$80.00 for Non-Members.

All registrations must be made on the official registration form obtainable from the Executive Office of the College, 4200 Pine St., Philadelphia 4, Pa.

#### SCHEDULE

No.	Title	Institution	Director	Dates
1.	Growth, Isotopes and Tumor Formation	Lankenau Hospital Research Institute, Philadelphia, Pa.	Dr. S. R. Reimann	February 3-8
2.	Cardiovascular Disease	University of Southern California School of Medicine, Los Angeles, Calif.	Dr. G. C. Griffith	February 3-8
3.	Peripheral Vascular Disease	Mayo Foundation, Univ. of Minn. Rochester, Minn.	Dr. E. V. Allen	March 17-22

No.	Title	Institution	Director	Dates
4.	Arthritis & Allied Conditions	Mayo Foundation, Univ. of Minn. Rochester, Minn.	Dr. P. S. Hench	March 24-29
5.	Cardiovascular Disease	Emory University School of Medicine, Atlanta, Ga.	Dr. R. Bruce Logue	March 31-April 5
6.	Internal Medicine	University of Michigan Medical School, Ann Arbor, Mich.	Dr. C. C. Sturgis	April 7-12
8.	Cardiovascular Disease	Northwestern University Medical School, Chicago, Ill.	Dr. J. Roscoe Miller	April 21-26 *
7.	Cardiovascular Disease	Philadelphia General Hospital, Philadelphia, Pa.	Dr. Francis C. Wood & Dr. Calvin Kay	May 12-17
9.	Internal Medicine	University of Cincinnati College of Medicine, Cincinnati, Ohio	Dr. M. A. Blankenhorn	May 26-June 7

\* Course No. 7 immediately precedes the A.C.P. Annual Session in Chicago, April 28- May 2.

#### THE COMMITTEE ON POSTWAR MEDICAL SERVICE NOW KNOWN AS JOINT COMMITTEE FOR THE COÖRDINATION OF MEDICAL ACTIVITIES

Early in World War II, The American College of Physicians, The American Medical Association, and The American College of Surgeons established a joint Committee on Postwar Medical Service. Representation on the Committee was soon extended to many other national medical and hospital organizations, and meetings have been held monthly through the intervening years. On October 12, 1946, the name of the Committee was changed to "The Joint Committee for the Coördination of Medical Activities," with the concurrence and approval of each participating organization.

During the War years, the Committee was concerned almost wholly with postwar planning. In recent months the Committee has been concerned with industrial health, physical fitness, and other matters on which discussions in a group of this sort should help to crystallize medical opinion. It is a joint committee concerned with medical planning, not active in itself until its associate organizations have concurred in planned proposals. Represented on the present Committee are the Offices of the Surgeons General of the U. S. Army, U. S. Navy, and U. S. Public Health Service, the Federation of State Medical Boards, the American and Catholic Hospital Associations, the Advisory Board for Medical Specialties, and several others.

The meeting of this Committee on October 12, 1946, covered discussions on the following subjects:

The Bureau of Information of the American Medical Association, re handling location problems of physician veterans; Surplus Property; Intern and Residency Opportunities; The Resident Program for Physician Veterans; Licensure; a Specialty Board for General Practitioners; Establishment of Medical Corps in Veterans' Administration; Rural Medical Service; Industrial Health; Physical Fitness; Automobile Priorities for Physicians; Data on Army Separations, etc.

#### REPORTS ON RECENT REGIONAL MEETINGS

##### *Chicago, November 16, 1946*

The Annual Regional Meeting of The American College of Physicians for the territory embracing Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota, and Wisconsin was held at the Congress Hotel, Chicago, November 16, 1946, with an attendance of 425 physicians. College Governors for the participating states acted as presiding officers and coöperated in the preparation of the program, selecting

speakers from each territory. The program, although limited to one full day of presentations, was considered an outstanding one, and this was borne out by the full attendance of physicians at every part of the program, continuing to the concluding paper. At the Luncheon Meeting Dr. LeRoy H. Sloan, F.A.C.P., Regent and General Chairman of the 1947 Annual Session of the College, spoke at length on the preparations for the meeting, details concerning the program, and other relevant matters. At the Dinner Meeting in the evening, at which numerous distinguished guests were present, Dr. David P. Barr, F.A.C.P., President of the College, made an address on the historical development and purposes of the College, and Dr. Andrew C. Ivy, F.A.C.P., Vice President and Distinguished Professor of Physiology, University of Illinois College of Medicine, and Assistant Dean of Northwestern University, gave an address on "War Crimes of a Medical Nature," his address dealing with the medical war crimes in Germany during the recent war.

*Memphis, Tenn., November 22, 1946*

A Regional Meeting of the College for the territory embracing Arkansas, Louisiana, Mississippi, Tennessee, and Texas was held at Memphis, November 22, 1946, under the Governorship of Dr. William C. Chaney of Memphis, with the cooperation of the College Governors for the other states. Dr. William D. Stroud, Philadelphia, gave an address on Coronary Artery Disease; Dr. Conley Sanford, F.A.C.P., Dr. William C. Colbert, F.A.C.P., and Dr. Douglas Sprunt, F.A.C.P., of the University of Tennessee College of Medicine, Memphis, conducted a Clinical Pathologic Conference; Dr. H. Packer of the Division of Preventive Medicine, University of Tennessee College of Medicine, gave an address on "New Knowledge in the Treatment of Malaria"; Dr. Walter L. Palmer, F.A.C.P., of the University of Chicago, The School of Medicine, made a presentation on "Treatment of Intractable Peptic Ulcer"; and Dr. Hugh Morgan, F.A.C.P., President-Elect of the College, and Professor of Medicine at Vanderbilt University, Nashville, gave a paper on "Hypertension." In the evening a dinner was given at the Memphis Country Club in honor of Dr. Hugh Morgan as President-Elect of the College. Mr. E. R. Loveland, Executive Secretary of the College, Philadelphia, presented a report on the activities of the College during the current year. Dr. William D. Stroud, F.A.C.P., Philadelphia, introduced Dr. Morgan who made a most interesting philosophical address on the professions, with special regard to medicine and the relationship of The American College of Physicians.

The scientific program was restricted to a small number of speakers but each speaker was given an adequate time to cover thoroughly his subject. The program was exceedingly well received and the attendance was approximately 300.

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Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, has announced that the Service will receive to May 1, 1947, applications from physicians for training in an accredited school of public health during academic year 1947-48. The purpose of the Fellowships is to provide trained health officers to fill the many vacancies which exist in state and local health departments. Full details may be secured from The Surgeon General, U. S. Public Health Service, 19th and Constitution Aves., N. W., Washington 25, D. C. (Attention Public Health Training.)

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In its seventh Annual Essay Contest, the Mississippi Valley Medical Society will offer a cash prize of \$100, a gold medal, and a certificate of award for the best unpublished essays on a subject of general medical interest and value to the general practitioner of medicine. Contestants must be members of the American Medical

Association and residents of the United States. The winner will be invited to present his contribution before the next annual meeting of the Society, which will be held at Burlington, Iowa, October 1-3, 1947. The Society reserves the right to publish the essays in its publication. Contributions should not exceed 5,000 words and should be submitted in quintuplicate not later than May 1, 1947, to Dr. Harold Swanberg, F.A.C.P., Secretary of the Society, 209-224, W.C.U. Bldg., Quincy, Ill.

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A meeting of the Antibiotics Study Section of the National Institute of Health will be held in Washington, D. C., January 31 and February 1, 1947. Representatives of Government agencies, commercial producers, and investigators concerned with antibiotics are invited to attend this conference. Expenses, unfortunately, cannot be defrayed by the Bureau of Public Health Service. Inquiries concerning the meeting and the presentation of scientific reports should be addressed to Dr. Gordon Seger, Executive Assistant, National Institute of Health, Bethesda 14, Md.

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Drs. Francis J. Braceland, F.A.C.P., Rochester, Minn., Arthur Carlisle Christie, F.A.C.P., Washington, D. C., and William S. Middleton, F.A.C.P., Madison, Wis., have been appointed members of a special advisory group concerned with assisting General Omar N. Bradley, Administrator of Veterans Affairs, and Dr. Paul R. Hawley, F.A.C.P., chief of the Veterans Administration's Department of Medicine and Surgery, in developing over-all policies for medical services.

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Dr. Julius Chasnoff, F.A.C.P., New York, N. Y., received the Army Commendation Ribbon for his services with the Thomas M. England General Hospital. The citation read in part, "service with the Medical Department has been exceptional when compared with others of the same grade of similar position, and I wish to commend you for your outstanding contribution as Chief of Medical Service, Executive Officer and President of the Army Retiring Board at the Thomas M. England General Hospital, Atlantic City, N. J., from October 1945, to May 1946."

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Speakers at the Fourth Annual Medical and Surgical Symposium, Watts Hospital, Durham, N. C., February 12, 1947, will include Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio; Dr. Monroe J. Romansky (Associate), Washington, D. C.; Dr. Howard F. Root, F.A.C.P., Boston; Dr. Albert M. Snell, F.A.C.P., Rochester, Minn.; and Dr. Francis C. Wood, F.A.C.P., Philadelphia.

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Brig. Gen. Robert M. Hardaway, U. S. Army, F.A.C.P., has been awarded the Legion of Merit. As commanding officer of the Bushnell General Hospital, August, 1942, to January, 1946, Dr. Hardaway is said to have "developed a superior program for amputee patients throughout the Ninth Service Command."

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Brigadier General Eugen C. Reinartz, formerly commandant of the AAF School of Aviation Medicine, Randolph Field, Texas, has retired from active duty with the Army after twenty-nine and a half years of service. He entered the Service in 1919, being assigned to the Aeronautics Division of the Aviation Section, Signal Corps, and had continuous service with aeronautics thereafter. He went to both the English and North African Theaters of War as aeromedical observer to study problems confronting flight surgeons in combat. He received the John Jeffries Award for exceptional contributions to the advancement of aeronautics through medical research, in 1943, the award being given by the Institute of Aeronautical Sciences. It is said he has had the longest continuous service of any medical officer in the Army Air Forces.



Col. Charles T. Young, U. S. Army (Associate), has received the Oak Leaf Cluster to the Legion of Merit. The citation related that as commanding officer of the Wakeman Convalescent Hospital, Dr. Young "displayed a high type of organizational ability and leadership."

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Dr. Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, has been awarded the Cross of the Legion of Honor from the French Government.

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Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, has been awarded the Officer's Cross of the Royal Order of Leopold the Second by the Prince Regent of Belgium. The award recognizes Dr. Geiger's "distinguished services rendered to Belgium and for unusual resourcefulness as an administrator of public health."

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Dr. Marcus A. Feinstein (Associate), of New York, N. Y., has been awarded the Army Commendation Ribbon. The commendation recognizes the valuable addition to medical knowledge from Dr. Feinstein's study of an outbreak of acute respiratory disease which occurred in bomber squadrons returned from overseas. Dr. Feinstein retired from the Army of the United States with rank of Major, April, 1946.

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Dr. Leon Unger, F.A.C.P., Chicago, was elected President of the American College of Allergists at its meeting in San Francisco last June.

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Dr. Virgil P. Sydenstricker, F.A.C.P., Augusta, Ga., has been awarded the King's Medal by King George VI. The award recognizes Dr. Sydenstricker's distinguished service to the British Government during World War II.

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Dr. William P. Corr, F.A.C.P., Riverside, Calif., who retired with rank of Colonel from the Medical Corps, Army of the United States, in January, 1946; has been awarded the Legion of Merit. The citation speaks of Dr. Corr's "meritorious service at Dibble General Hospital, Menlo Park, Calif., from October 1943 to June 1945," his "wide knowledge of all phases of internal medicine, quiet yet forceful leadership and high ideals . . . administrative ability."

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#### ADMIRAL MCINTIRE RETIRES FROM POST OF SURGEON GENERAL

It was recently announced that Vice Admiral Ross T. McIntire, F.A.C.P., had retired from the position of Surgeon General of the U. S. Navy, and would shortly retire from the Service. Dr. Clifford A. Swanson has been appointed by the President to succeed Dr. McIntire, with rank of Rear Admiral.

Dr. McIntire received his M.D. degree from Willamette University in 1912. He entered the Medical Corps of the Navy in 1917, and became Surgeon General in 1939. Dr. McIntire's administrative ability and professional zeal are said to have contributed largely to the effectiveness of the Bureau of Medicine & Surgery in preparing for and dealing effectively with the medical problems of the past war.

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#### DR. ROBERT B. RADL, F.A.C.P., BISMARCK, N. D., APPOINTED A.C.P. GOVERNOR FOR NORTH DAKOTA

Owing to the recent death of Dr. Julius O. Arnson, College Governor for the State of North Dakota, and in accordance with provisions of the Constitution and By-Laws, Dr. David P. Barr, President, has appointed Dr. Robert B. Radl, F.A.C.P., Bismarck, as interim Governor to complete the unexpired term of the late Dr. Arnson.

## RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to December 13, 1946 inclusive).

William B. Adamson, Abilene, Tex. (Lt. Col., MC, AUS)  
 George R. Callender, Washington, D. C. (Brig. Gen., MC, USA)  
 Everett LeCompte Cook, Martinsburg, W. Va. (Col., MC, USA)  
 W. Lee Hart, Dallas, Tex. (Brig. Gen., MC, USA)  
 Ellis H. Hudson, Athens, Ohio (Capt., MC, USNR)  
 Noble D. Leonard, Downey, Ill. (Capt., MC, USNR)  
 George L. Leslie, Howell, Mich. (Lt. Col., MC, AUS)  
 Adolph B. Loveman, Louisville, Ky. (Major, MC, AUS)  
 Eugen G. Reinartz, San Francisco, Calif. (Brig. Gen., MC, USA)  
 Paul B. Roen, Los Angeles, Calif. (Comdr., MC, USNR)  
 William H. Roper, Denver, Colo. (Major, MC, AUS)  
 Joseph M. Ryan, Oak Ridge, Tenn. (Lt. Col., MC, AUS)  
 Paul L. Shallenberger, Chicago, Ill. (Col., MC, AUS)  
 Norman S. Skinner, Saint John, N. B., Can. (Major, RCAMC)  
 Arthur G. Sullivan, Hot Springs National Park, Ark. (Comdr., MC, USNR)  
 Julius Wolfram, Dallas, Tex. (Capt., MC, AUS)

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Correction

It was erroneously stated in the August issue (page 391) that Dr. Julius Chasnoff, F.A.C.P., retired from the Army Medical Corps prior to July 12, 1946, with rank of Lieutenant Colonel. Dr. Chasnoff's separation from the service was completed November 2, 1946; at that time he held the rank of Colonel.

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MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA., OCTOBER 20, 1946

The regular autumn meeting of the Board of Regents was held at the College Headquarters, Philadelphia, October 20, 1946, with President David P. Barr presiding and Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

David P. Barr .....	<i>President</i>
Hugh J. Morgan .....	<i>President-Elect</i>
James J. Waring .....	<i>First Vice President</i>
A. B. Brower .....	<i>Second Vice President</i>
William D. Stroud .....	<i>Treasurer</i>
George Morris Piersol .....	<i>Secretary-General</i>
Charles T. Stone .....	
Walter B. Martin .....	
William S. Middleton .....	
James E. Paullin .....	
LeRoy H. Sloan .....	
George F. Strong .....	
William S. McCann .....	
T. Grier Miller .....	
Charles F. Moffatt .....	
Maurice C. Pincoffs .....	<i>Editor, ANNALS OF INTERNAL MEDICINE</i>
Chauncey W. Dowden .....	<i>Chairman, Board of Governors</i>
Edward L. Bortz .....	<i>Chairman, Advisory Committee on Post-graduate Courses</i>

The Secretary read abstracted Minutes of the preceding meetings of the Board of Regents, which were approved as read.

The Secretary then read communications from various members of the Board of Regents who could not be present, and from the following:

- (1) Dr. Ward Darley, F.A.C.P., Denver, Colo.—asking the College to consider ways and means of making it possible for members of the College to deduct from Federal Income Tax Returns expenses incurred as a result of attending Postgraduate Courses conducted by the College.  
It was the opinion of the Board that this matter ought to be handled individually in different districts, and should be taken up directly with the local Collector of Internal Revenue.
- (2) Dr. David P. Barr, F.A.C.P., New York, N. Y., President—reporting that Dr. G. Gill Richards, F.A.C.P., Salt Lake City, Utah, had been the official representative of the American College of Physicians at the inauguration of the new President of the University of Utah.
- (3) Dr. David P. Barr, F.A.C.P., New York, N. Y., President—reporting that Dr. Nelson G. Russell, Sr., Buffalo, N. Y., had been the official representative of the American College of Physicians at the Centennial Celebration of the University of Buffalo, October 3-4, 1946.
- (4) Dr. David P. Barr, F.A.C.P., New York, N. Y. President—reporting that Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, Ohio, has been appointed as official representative of the College at the proposed meeting of the International Congress of Tropical Medicine and Malaria, to be held in the United States at an early date.
- (5) Dr. Herman H. Riecker, F.A.C.P., Ann Arbor, Mich.—giving details of the last illness of the late Dr. James D. Bruce and concerning a floral tribute supplied at his funeral on behalf of the College.
- (6) Dr. George D. Mallory, Assistant Secretary, University of California—acknowledging receipt of and expressing the gratitude of the Regents of the University for a check for \$3,840.00, representing tuition fees collected by the College for a Postgraduate Course at that institution during June, 1946.
- (7) Dr. Alexander H. Colwell, F.A.C.P., Pittsburgh, Pa.—requesting permission for one or more medical residents to attend the annual meeting of the American College of Physicians.  
Dr. Colwell had already been informed that the College would be pleased to grant them the courtesy of admission.
- (8) The Executive Office of the College—notifying members of the Board of the privilege to obtain Air Travel Cards for official College travel.
- (9) A Regent of the College—quoted partially as follows: "What are we doing as a College to insure that our members are keeping up with progress in medicine? How many of them are getting about and trying to absorb a bit more of the cheapest commodity on the present market? Why should not the College sponsor a concentrated course for members of the Board of Regents and Board of Governors, which would include only the very newest in medical research and progress? Then why not sponsor a series of publications, to be distributed to members only, in the form of question and answer, which would cover in the period of three months the whole field of the newer chemistry, biology, physiology, pathology, etc., related to Internal Medicine. . . ."

President Barr stated that the new College Marshal, Dr. T. Grier Miller, Philadelphia, would appreciate suggestions from the Board about the conduct of the Convocation, and stated that he had in mind some changes that would be helpful.

*Report of the SECRETARY-GENERAL—Dr. George Morris Piersol: "The following 35 Fellows and 6 Associates have died since the last meeting of this board:*

*Fellows*

Anderson, William Wesley	Fort Thomas, Ky.	April 2, 1946
Barnhart, Grant Samuel	Washington, D. C.	July 25, 1946
Baxmeier, Robert Ivan	Pittsburgh, Pa.	June 27, 1946
Bertolet, William S.	Reading, Pa.	October 9, 1946
Bisaillon, Marr	Portland, Ore.	June 3, 1946
Bissell, Wayne W.	Rockford, Ill.	September 6, 1946
Bruce, James D.	Ann Arbor, Mich.	September 5, 1946
Carr, Earl Curtis	M.C., U. S. Navy	May 9, 1946
Chase, Harrison A.	Falmouth, Mass.	July 23, 1946
Cohen, Mortimer	Pittsburgh, Pa.	June 20, 1946
Craven, Erle Bulla, Jr.	Lexington, N. C.	June 19, 1946
Dozzi, Daniel Louis	Philadelphia, Pa.	May 18, 1946
Foster, Benjamin B.	Portland, Maine	May 8, 1946
Frick, Anders	Chicago, Ill.	May 9, 1946
Gordon, Murray B.	Brooklyn, N. Y.	June 29, 1946
Holmes, Champneys Holt	Atlanta, Ga.	June 12, 1946
Huber, Edward	M.C., U. S. Army	July 23, 1946
Jensen, Walter Steen	M.C., U. S. Army	April 4, 1946
Levy, I. Harris	Syracuse, N. Y.	July 9, 1946
Libman, Emanuel	New York, N. Y.	June 28, 1946
MacNeal, Ward J.	New York, N. Y.	August 15, 1946
McGovern, Louis Vincent	Brooklyn, N. Y.	April 29, 1946
Moyer, Torrence C.	Lincoln, Nebr.	September 8, 1946
Palmer, Donald Ainslie	Spokane, Wash.	June 10, 1946
Scott, W. Mastin	Shreveport, La.	July 21, 1946
Smith, Eben Elliott	M.C., U. S. Navy	June 16, 1946
Soiland, Albert	Los Angeles, Calif.	May 14, 1946
Solway, Leon Judah	Toronto, Ont., Canada	December 14, 1945
Spangelberger, Mathew Arnold	Denver, Colo.	June 9, 1946
Spector, Hyman I.	St. Louis, Mo.	July 6, 1946
Stevens, Rollin H.	Detroit, Mich.	May 17, 1946
Thomas, John D.	Washington, D. C.	July 15, 1946
Twyman, George Thomas	Independence, Mo.	October 4, 1946
Wilcox, Clark Anson	Wichita Falls, Tex.	April 4, 1946
Wilson, Robert, Sr.	Charleston, S. C.	May 20, 1946

*Associates*

Barnes, James R. E.	Cicero, Ill.	June 16, 1946
Barthelme, Francis Lorraine	Effingham, Ill.	March 8, 1946
Curry, Grove P. M.	Mount Kisco, N. Y.	May 13, 1946
Kirkland, Clyde W.	Bellaire, Ohio	March 25, 1946
Morris, Alanson F. B.	Pittsburgh, Pa.	February 6, 1946
Scott, Joseph Eckles	Portland, Ore.	April 23, 1946

On the occasion of Dr. Bruce's death, President Barr, Secretary Loveland and others, wrote personal letters to Mrs. Bruce, and an appropriate floral tribute was furnished through Dr. Herman H. Riecker on behalf of the Officers, Regents and Governors of the College. Do you not think we should have a resolution inserted in the Minutes which shall also go to Dr. Bruce's family?"

... On motion by Dr. Hugh J. Morgan, seconded by Dr. Charles T. Stone, and carried, a resolution was adopted approving the above, and President Barr requested

Dr. Hugh J. Morgan to prepare such a resolution for insertion in the Minutes and transmission to Mrs. Bruce. . . .

. . . A special notice was also taken on the death of Dr. Robert Wilson, Sr., Charleston, S. C., who was formerly a Governor of the College. . . .

"Since the last meeting of the Board, the following additional 5 Fellows have become Life Members of the College, bringing the grand total to 493, of whom 42 are deceased, leaving a balance of 451:

Leo E. Westcott	Kalamazoo, Mich.
Morris Deitchman	Youngstown, Ohio
Arthur Ernest Moon	Temple, Tex.
George Foster Herben	Yonkers, N. Y.
Gustav Leonard Kaufmann	Chicago, Ill.

. . . On motion by Dr. James E. Paullin, seconded by Dr. George F. Strong, and carried, the report of the Secretary-General was accepted. . . .

*Report of the EXECUTIVE SECRETARY*—Mr. E. R. Loveland: "Practically all items that would be included in the Executive Secretary's Report will be brought out through Committee deliberations and reports following. Our Regional Meeting program received such a stimulus during the War that it is continuing with the same enthusiasm and interest. It was our thought that after our Annual Sessions are resumed emphasis would be placed primarily on State Regional Meetings, which have a real value in a more intimate and personal way than the larger multi-State meetings. However, there is a tendency for the Governors to continue their multi-State plan in many instances. The following is the schedule of meetings already held or planned:

Territory	City	Date	Chairman
Western Pennsylvania	Pittsburgh	Sept. 11, 1946	R. R. Snowden
Virginia	Virginia Beach	Oct. 15, 1946	J. W. Preston
Western New York	Syracuse	Oct. 16, 1946	E. C. Reifenstein, Sr.
North Carolina	Winston-Salem	Oct. 18, 1946	P. F. Whitaker
			E. L. Persons
Western Michigan	Grand Rapids	Oct. 30, 1946	B. R. Corbus
Florida, Alabama, Georgia, and South Carolina	Miami Beach	Nov. 3-4, 1946	T. Z. Cason
New Jersey	Newark	Nov. 8, 1946	G. H. Lathrope
Illinois, Indiana, Iowa, Ken- tucky, Michigan, Minnesota and Wisconsin	Chicago	Nov. 16, 1946	W. L. Palmer
Tennessee	Memphis	Nov. 22, 1946	W. C. Chaney
New England	Hanover, N. H.	Jan. 28, 1947	H. T. French
Eastern Pennsylvania and Delaware	Philadelphia	Feb. 7, 1947	E. L. Bortz
Oklahoma	Oklahoma City	Feb. 22, 1947	Wann Langston

There is a definitely growing interest in College membership, with an ever-increasing number of inquiries and proposals for membership. I predict there will be no less than 350 candidates for Associateship and 250 candidates for Fellowship. The last meeting of the Board of Regents being held late in the spring (May, 1946) and this autumn's meeting being held much earlier than usual created a much shorter period between meetings than customary. Even so we have prepared for the Credentials Committee 108 candidates for Fellowship and 183 candidates for Associateship. It must be remembered that the intervening period has been primarily a summer season, too.

There is a tremendous increase in College work. More than 30,000 inquiry cards have been mailed out this year concerning candidates. Especially has the ANNALS OF INTERNAL MEDICINE forged ahead in popularity, both as a scientific journal and as an advertising medium. The advertising volume has

increased 60% since July 1, 1939; the circulation has increased 85% since July 1, 1939, a considerable proportion of this being during the past year. Contrary to our anticipation that with the ending of the War, the Army and Navy would discontinue their orders and the circulation would fall off, the Army and Navy have continued a fair proportion of their orders, and the profession has greatly multiplied its number of subscriptions. 1946 income from subscriptions will be over \$53,000.00, which means the handling of more than 9,000 individual subscription items. The advertising income will be nearly \$22,000.00, which represents the handling of many different accounts. As a matter of fact, the business now entailed in handling the "Annals" alone greatly excels all the business combined in the College a few years back. Publishing Regional Meeting programs and forms and arranging the details likewise entail a real extension in the work of the College.

I am gratified to report that we have an improved office personnel over that of the past two or three years. There is an improvement in the type and in their ability, and Mr. Pindar, who is now with us on full time, is establishing a promising record."

... The Executive Secretary's report was opened for discussion. Dr. LeRoy H. Sloan, a member of the Committee on Credentials, pointed out that there is a tremendous amount of work and expense involved in handling the inquiry cards on candidates, and that a fairly large proportion are returned as "unknown." He suggested it is time to consider some other technic of obtaining information about candidates, such as the establishment of a Committee of the Governors, or some other means. Mr. Loveland stated that the card system works wholly satisfactorily in smaller States and smaller communities and has a definite value, but that in large communities, such as New York City, there is such a large number of members that, obviously, candidates are known to a comparatively small percentage thereof. However, the card system is provided for in our By-Laws and on our proposal form. . . .

... On motion by Dr. James E. Paullin, seconded by Dr. Hugh J. Morgan, and carried, it was

RESOLVED, that this question be referred to the Committee on Credentials, to report some recommendation at a later date.

*Report of the COMMITTEE ON CREDENTIALS*—Dr. George Morris Piersol, Chairman: "The Committee on Credentials reviewed the proposals of 108 candidates for Fellowship and 183 candidates for Associateship. An analysis of its recommendations is as follows:

(A) Candidates for FELLOWSHIP:

Recommended for Advancement to Fellowship .....	59
Recommended for Election Directly to Fellowship .....	14
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Recommended for Election First to Associateship .....	3
Deferred .....	31
Rejected .....	1
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Total .....	108

(B) Candidates for ASSOCIATESHIP:

Recommended for Election .....	123
*Fellowship Candidates Recommended for Election first to Associateship .....	3
Deferred .....	43
Rejected .....	17
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183, plus \*3

The Committee, therefore, recommends the election of the following 73 candidates to Fellowship. (List published in the November, 1946, issue of this journal.)

... On motion by Dr. George Morris Piersol, seconded by Dr. William D. Stroud, and carried, the above 73 candidates were formally elected to Fellowship. ...

"The Committee recommends the election of the following 126 candidates to Associateship. (List published in the November, 1946, issue of this journal.)

... On motion by Dr. James E. Paullin, seconded by Dr. William D. Stroud, and carried, the above 126 candidates were officially elected to Associateship. ...

"The Credentials Committee submits the following report on candidates elected to Associateship five years ago, December 14, 1941:

Already Advanced to Fellowship .....	57
Deceased .....	1
Dropped for Failure to Qualify for Advancement to Fellowship .....	12
Time Extended because of Military Service .....	30
	<hr/>
	100

The following Associates from the Class of December 14, 1941, are entitled to a certain extension of time, due to military service:

Allday, Louis Edgar	Dallas, Tex.
Burket, L(ouis) Clair	Altoona, Pa.
Caldwell, John W. G.	Des Moines, Iowa
Carson, Leon Delwin	M. C., U. S. Navy
Chapman, Kenneth William	U. S. Public Health Service
Davis, John Kemp	M. C., U. S. Army
Foster, William Bell	M. C., U. S. Army
Green, Eugene Willard	U. S. Public Health Service
Kilgore, Floyd Vern	M. C., U. S. Army
Kilgore, Newton Alvin, Jr.	Houston, Tex.
Lawson, Dwight	M. C., U. S. Army
Liston, David Ernest	M. C., U. S. Army
Lyman, Harold Dwight	U. S. Public Health Service
Main, Emory Hendon	Philippi, W. Va.
McCarty, David Wilson, Jr.	Longmont, Colo.
Morrison, Albert Taylor	U. S. Public Health Service
Nelson, Kenneth Roy	U. S. Public Health Service
Ossenfort, William Frederick	U. S. Public Health Service
Pinckney, Norton Morris	Richmond, Va.
Power, Frank Kenneth	Salem, Ore.
Price, Frank Lewis	U. S. Public Health Service
Rinck, Edward Clinton	U. S. Public Health Service
Royce, Owen, Jr.	Milwaukee, Wis.
Shallenberger, Paul Lawrence	Chicago, Ill.
Stone, Robert Edwards,	Birmingham, Ala.
Telfer, James Gavin	U. S. Public Health Service
Vaughn, John Orren	Santa Monica, Calif.
Vogel, Stoughton Ralph	Philadelphia, Pa.
Voorhies, Norton William	New Orleans, La.
Wallace, C(harles) Stewart	Ithaca, N. Y.

Twelve Associates who were not on military service have not fulfilled the requirements and under conditions of the By-Laws must now be dropped.

The Credentials Committee has seriously taken up the question of the use of the

inquiry cards concerning candidates, and it would welcome suggestions or any plan from any member of the Board of Regents. The present system is very expensive, unwieldy and not too successful."

... By resolution the report of the Committee on Credentials was accepted as a whole. ...

*Report of the COMMITTEE ON SURVEY*—Dr. William S. Middleton, Chairman: "The Regents will recall that there were a number of suggestions involved in the task of the Survey Committee, largely to reconcile and clarify the requirements for Fellowship and Associateship. It also undertook to insert into the Constitution and By-Laws a clause that would implement Mastership.

## ARTICLE V

### ELECTION OF FELLOWS

*Section 1.* A Fellow of the College shall have met the following qualifications and requirements:

(a) He shall have qualified and served a minimum period of three years as an Associate, except upon recommendation of the Committee on Credentials by reason of very special qualifications as hereinafter set forth.

(b) He shall have been graduated from a medical school acceptable to the Board of Regents, at least five years prior to the time of his election, and if engaged in practice, his professional activity must be confined to the field of internal medicine or a related specialty.

(c) If he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of internal medicine or an allied specialty at a permanent location for at least three years preceding nomination for Fellowship. The Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify this ruling under exceptional conditions.

(d) The criteria of eligibility for election to Fellowship are bi-lateral:

1. Detailed information concerning the candidate's hospital and academic appointments, with particular reference to the size and nature of the hospital service and the exact teaching responsibility; published contributions in media acceptable to the Committee on Credentials, with particular emphasis upon papers published during the period of Associateship; personal approval by Fellows in his territory, with reference to his character, ethical standing and medical activities; evidence of postgraduate training and attendance upon the Annual Meetings of the College.

2. He shall be certified by the recognized national board of certification in his particular field, where such an accrediting board exists. This regulation, however, shall not apply to candidates from civilian life who were elected to Associateship prior to April 6, 1940, nor to such candidates from the Army, Navy and Public Health Service who were elected prior to and including April 1, 1944.

### PROPOSAL

*Section 2.* His name shall be proposed in writing by a Master or Fellow of the College from the same state, province or territory, not an officer or member of the Board of Regents; he shall be seconded by another Master or Fellow from the same state, province or territory and endorsed by the member of the Board of Governors from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service or the Medical Director of the Veterans Administration, or by an officer of the College or by a member of the Board of Regents. His nomination must be accompanied by an adequate written statement made both by the proposer and the seconder, containing all of the above cited qualifications of



the candidate. Furthermore, the name of the candidate shall be sent to each Fellow in the Candidate's locality with the request for comments as to the candidate's fitness. The proposer must be prepared to add such further information as may be requested by the Committee on Credentials.

*Section 3.* The credentials of the candidate shall be considered by the Committee on Credentials, which Committee shall report to the Board of Regents for election or rejection.

Successful candidates shall be so notified immediately after their election and shall be urged to attend the next succeeding Convocation, when Fellowships will be formally conferred. The official Fellowship Certificate, signed by the President and the Secretary-General, shall be issued following the Convocation. Acknowledgment of its receipt shall be made upon an official card, signed and dated by the newly elected Fellow, and returned to the Executive Secretary, to be added to the official College roll.

*Section 4.* Proposals for direct election to Fellowship, with or without prior certification by the appropriate certifying board, may be made to the Committee on Credentials. This manner of election is an unusual mark of distinction; hence such candidates must be preëminent in teaching, research or clinical practice. In advancing individuals for such consideration, the following details must be furthermore considered: maturity, national reputation, publications and other contributions to medical science and public welfare. The Committee on Credentials will exercise due discrimination in all proposals for direct election to Fellowship.

This ruling will not be invoked for candidates who have failed of regular advancement from Associateship to Fellowship.

## ARTICLE VI

### ELECTION OF MASTERS

*Section 1.* A special committee on Masterships will be named by the President. This committee will consist of two members from the Board of Regents and one member from the Board of Governors. It will bring its nominations of Master to the Board of Regents for election or rejection.

## ARTICLE VII

*Section 1.* An Associate of the College shall have met the following qualifications and requirements:

(a) He shall hold the degree of M.D., M.B., or M.D., C.M., from a medical school acceptable to the Board of Regents.

(b) After receiving his medical degree, the candidate shall have had at least one year internship in an approved hospital and three years of organized graduate training in internal medicine or allied fields, or its equivalents, approved by the Committee on Credentials and the American Board of Internal Medicine. One year of this graduate training may be spent in the basic sciences.

(c) He shall be a member in good standing in his local, state, provincial or territorial and national medical societies, except in the case of those not engaged in practice, such as full-time teachers, research workers, and those holding official hospital and similar positions.

(d) If a practitioner, he shall be licensed to practice medicine in his state, province or territory, and shall indicate his purpose to confine his practice to internal medicine or an allied specialty from the date of his application, or be a Medical Officer in the Government Service, either in the United States or the Dominion of Canada, in American or Foreign Service. If not a practitioner, he shall hold an official in-

stitutional position in internal medicine, an allied branch of internal medicine or in medical research.

### PROPOSAL

*Section 2.* His name shall be proposed on the official blank of the College by a Master or Fellow residing in the same state, province or territory, not an officer or member of the Board of Regents; he shall be seconded by another Master or Fellow also from the same state, province or territory, and endorsed by the member of the Board of Governors from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service or the Medical Director of the Veterans Administration; or in special instances, by an Officer of the College or by a member of the Board of Regents.

*Section 3.* The credentials of candidates for Associateship shall be considered first by the Committee on Credentials, which Committee shall report to the Board of Regents for election or rejection.

Successful candidates shall receive at once, from the Board of Regents through the Executive Secretary, an appropriate official notification of their election to Associateship in the College.

### TERM OF ASSOCIATESHIP AND ELIGIBILITY FOR FELLOWSHIP

*Section 4.* Candidates so elected shall be continued as Associates for a term not to exceed five years.

The Associate will be eligible for election to Fellowship at the end of three years. Upon expiration of this three year period he shall be notified in writing by the Committee on Credentials of his eligibility for election to the Fellowship during the next two years, provided he has met the requirements necessary for Fellowship within that time. If he is not elected to Fellowship within five years, his Associateship is automatically terminated. The Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify this ruling under exceptional conditions."

... The report was opened for general discussion. In regard to certification, it was pointed out that Canadian candidates, under the new provisions, by referring to "National" instead of "American" may qualify through certification by the Royal College of Physicians of Canada, and that candidates from the Caribbean and Central American countries would have to satisfy the standards of the United States. Dr. Strong referred to a number of Canadian physicians who have qualified as Fellows of the Royal College of Physicians of London, whose examinations are reported to be much more difficult than those in the United States, and inquired whether there is any provision to cover these men. Dr. Middleton said there was none, that the Survey Committee felt the machinery within the Dominion of Canada would take care of such cases, especially if reciprocal recognition exists. Dr. Strong replied that such reciprocal recognition would be established in Canada.

Dr. LeRoy H. Sloan inquired, if criteria for election to Fellowship are bi-lateral, is a physician who is not certified by his Board ever eligible? Dr. Middleton replied that he may be eligible for direct election, and referred to that section dealing with proposals for direct Fellowship. Dr. Sloan further inquired about a physician who becomes an Associate of the College and thereafter turns to full-time teaching or research, for which there is no certifying board. Dr. Middleton replied that he could still qualify for Fellowship under the new regulations, without certification.

President Barr inquired about the case of the internist in small towns. Dr. Middleton stated that the Committee realized fully that many of these men would

be excluded, because they will be doing some obstetrics, minor surgery, etc., and that the Committee thought unquestionably the College would wish to discriminate between the man who is practicing general medicine and the one who is truly an internist. Dr. Piersol pointed out that the Credentials Committee is confronted frequently with the problem of the candidate who is essentially an internist, but who does general practice, some obstetrics and some limited surgery. The Committee considers that they do not fall within the proper category of the definition of an internist, and he expressed the belief that this provision is a wise one. Dr. Middleton further pointed out that this regulation was put in because the Committee on Credentials feels that this is the time at which the candidate should be apprised of the ideals of the American College of Physicians. It should define clearly at the outset of a candidate's entrance as an Associate whether or not he is going to be a general practitioner or an internist.

Dr. James J. Waring inquired about the significance of the term "allied specialty." Dr. Middleton pointed out that the College numbers among its members many specialists other than internists, such as Pediatricians, Neuropsychiatrists, Laboratorians, Dermatologists and Radiologists, and that this term refers to them.

Dr. Piersol suggested that inasmuch as this proposal by the Committee on Survey will be published to the members that the same clause which now exists in the By-Laws, namely, that election of a Fellow shall be in accordance with the By-Laws as stated and such additional rules of the Board of Regents that they from time to time may adopt, shall be inserted. This provision has proved most valuable and it provides for modification of the rules by action of the Board of Regents without the formal process of amending the By-Laws. Dr. Middleton stated this suggestion was acceptable.

. . . On motion by Dr. Hugh J. Morgan, seconded by Dr. William D. Stroud, and regularly carried, the report of the Committee on Survey was accepted, and it was planned that the proposal be circulated to all members of the Board of Regents and Board of Governors before the next joint meeting of those Boards.

Dr. Hugh J. Morgan spoke at length on behalf of the general practitioner, whose allegiance by and large is to the College in terms of interest and aspirations, but whose practice at the moment precludes him from College membership. He requested the Board of Regents to consider in the broad planning whether there is a role which the College can play in relation to the general practitioner. He said that in the group of general practitioners there is a small, but very important segment that aspires to quality, that looks to this College for help, stimulation and instruction. Dr. Morgan suggested the consideration of whether or not there might not be in the College not only the present group who can qualify for Fellowship, but a group of general practitioners of higher attainments who might be admitted to some Associate classification, and through that association the College might perform a fine function toward encouraging quality performance among a very important group of general practitioners.

Dr. Maurice C. Pincoffs supported Dr. Morgan's thought, but pointed out that it would be extremely difficult to set up differentials between the man who was described by Dr. Morgan and the present group who qualifies for regular membership. Furthermore, that it would include such a large number that the Annual Sessions of the College might be impossible to accommodate, physically and educationally.

*Report of the COMMITTEE ON PUBLIC RELATIONS*—Dr. James E. Paullin, Acting Chairman, in the absence of Dr. Roger I. Lee, Chairman: "The Committee has four communications:

- (1) Dr. Ross G. Harrison, National Research Council, informing the College of and asking its participation in the United Nations Educational, Scientific and Cultural Organization, which has to do with the further establishment of peace.

The Committee feels this communication should be received as information and referred to the Executive Committee of the College for proper answer.

- (2) Dr. W. C. Nalty, F.A.C.P., desiring the College to take some action whereby Fellowship in the College shall be recognized as equivalent to certification, entitling College members in the Veterans Administration to receive 25% increase in pay.

The Committee on Public Relations feels that this is not within the province of the College, and we recommend that Dr. Nalty be informed to that effect.

- (3) Dr. Malcolm T. MacEachern, F.A.C.P., American College of Surgeons, Chicago, Ill., calling attention to the existence of unrest in the world today about the division between physicians, surgeons and general practitioners.

This communication was received as information.

- (4) Dr. G. V. Brindley, seeking approval of the College of the resident training program of a Texas hospital.

Inasmuch as the College has established no department for this purpose, the Committee recommends this communication be referred to the Council on Medical Education and Hospitals of the American Medical Association."

... On motion by Dr. James E. Paullin, seconded by Dr. Hugh J. Morgan, and carried, this portion of the Committee's report was accepted and approved. ...

"The Committee recommends the acceptance of the following resignations:

1. Dr. Stephen L. Lirot (Associate), Meriden, Conn.
2. Dr. Floyd C. Taggart (Associate), Topeka, Kan.
3. Dr. M. J. Tornatore (Associate), Clearfield, Pa."

... On motion by Dr. James E. Paullin, seconded by Dr. William D. Stroud, and carried, this recommendation was approved and the resignations accepted. ...

"The Committee on Public Relations reviewed the following cases affecting fees and dues:

- (1) *Dr. Charles A. Breck, F.A.C.P., Wallingford, Conn.*

Due to total disability and inability to engage in practice, the Committee recommends that his dues be waived, and that he be given the privilege of deferment in the payment of his original Initiation Fee until his return to work."

... On motion by Dr. James E. Paullin, seconded by Dr. Maurice C. Pincoffs, and carried, this action was approved. ...

- "(2) *Col. Elias Earle Cooley, F.A.C.P., (MC), USA, Retired.*

The Committee recommends that because of physical disability, his dues be waived until resumption of remunerative work."

... On motion by Dr. James E. Paullin, seconded by Dr. James J. Waring, and carried, this motion was approved. ...

- "(3) *Capt. W. A. Vogelsang, F.A.C.P., (MC), USN, Retired.*

The Committee recommends that his dues be waived so long as he is not in active practice, or until he resumes remunerative work."

... On motion by Dr. James E. Paullin, seconded by Dr. Hugh J. Morgan, and carried, this recommendation was approved. ...

"The Committee had before it the disciplinary case of Dr. \_\_\_\_\_ (Associate), Ala., who became an Associate of the College by virtue of former membership in the American Congress on Internal Medicine. He has been convicted

of avoidance of payment of income tax, sentenced to the Federal Penitentiary and fined a large sum of money. We hold a copy of his indictment from the U. S. Court and the judgment and his commitment. The Committee recommends that he be summarily dropped from the College roll."

. . . On motion by Dr. James E. Paullin, seconded by Dr. Hugh J. Morgan, and carried, this recommendation was unanimously approved. . . .

"The Committee had some deferred business. On November 18, 1945, the Board of Regents referred to the Committee a consideration of whether to extend College membership beyond North America and its possessions. The present policy is to restrict membership to North American Countries and their dependencies, and, further, to physicians who read and speak English. The College has no machinery, under its present By-Laws, whereby candidates from other countries can qualify through our proposal system. On May 14, 1946, by resolution, without prejudice, this item of business was continued on the agenda of the next meeting of the Committee on Public Relations. The Committee at its meeting yesterday recommended that the membership of the College be restricted to its present boundaries, and that this matter be continued for future consideration by the Board of Regents."

. . . On motion by Dr. James E. Paullin, seconded by Dr. Charles T. Stone, and carried, the last recommendation on deferred business was approved, and the report as a whole was accepted. . . .

*Report of the COMMITTEE ON CONSTITUTION AND BY-LAWS*—Dr. James E. Paullin, Chairman: "There was referred to the Committee, consisting of Doctors Moffatt, Strong and Paullin, an amendment to the By-Laws, Article IV, Section 2, concerning the tenure of office of members of the Board of Governors. The Board of Regents on May 17, 1946, adopted a resolution providing that a proper by-law be prepared, providing for the limitation in the term of office of members of the Board of Governors to three consecutive terms of three years each, and that this by-law be presented for adoption at the next Annual Business Meeting of the College. To that end, the Committee recommends that the following added paragraph be made to Article IV, Section 2: 'The members of the Board of Governors shall each serve for a term of three years, and not more than three consecutive terms.'"

. . . On motion by Dr. James E. Paullin, seconded by Dr. William D. Stroud, and carried, the recommendation was approved. . . .

*Report of the COMMITTEE ON FELLOWSHIPS AND AWARDS*—Dr. James J. Waring, Acting Chairman, in the absence of Dr. Reginald Fitz, Chairman: "A lengthy report has been submitted by the Chairman, Dr. Fitz, which has received the careful consideration of the Committee. Research Fellowships in the past have been from one to three Research Fellows. Your Committee recommends this year that beginning July 1, 1947, an appropriation of \$20,000.00 be made to guarantee not more than eight Research Fellowships, each to last for twelve months, at a stipend of \$2,200.00 to \$3,000.00. The old range of stipend was \$1,800.00 to \$2,500.00. The Committee at the insistence of Dr. Fitz recommends certain changes in phraseology in the paragraph of the Directory, referring to Research Fellowships, the revised copy to be as follows:

'In line with one of the objects of the American College of Physicians to promote and advance clinical research, on October 20, 1946, by resolution, the Regents of the College established eight Research Fellowships of the American College of Physicians in the amount of \$2,200.00 to \$3,000.00 to be awarded each year until further notice on the recommendation of the Committee on Fellowships and Awards and the approval of the Board of Regents. These fellowships are designed especially for the benefit of young physicians who are in the early stages of preparation for a teaching and investigative career in medicine.

'The Committee on Fellowships and Awards obtains its list of candidates by communicating with the Professors of Medicine and Pediatrics in the approved

medical schools of the country and with the Officers and members of the Board of Regents of the College. The Committee may also utilize, to such extent as it deems wise, the machinery of the National Research Council.'

"The Committee offers this modification in the belief that the description of the Research Fellowships as it has been printed in the Directory of the College is no longer complete, that the stipend originally offered is now too meager, and that the appointment of more than one Research Fellow of the College each year is at present desirable. The Committee recognizes that if this recommendation is adopted, the annual expenditure of approximately \$20,000.00 of our income for this purpose must be authorized.

*"The James D. Bruce Fund*—it will be recalled that \$10,000.00 was donated by the late Dr. Bruce, half to be allocated for a memorial to Dr. Alfred Stengel and half to an Annual Lectureship in Preventive Medicine. On May 12, 1946, the Board of Regents directed the Committee to confer with the President and Secretary-General for the purpose of setting up the James D. Bruce Fund and establishing policies and principles regarding its use.

"The Committee on Fellowships and Awards believes an Annual Lectureship in Preventive Medicine, named for Dr. Bruce, would be in accord with his wishes, would be a suitable memorial to him as a Fellow always deeply interested in the welfare of the College, and that such a lectureship would add to the interests of our Annual Sessions. The John Phillips Memorial Award was set up in 1929; it was first a money award and later changed to a medal. The Committee on Fellowships and Awards has authority, after due consultation with certain authorities, to make the selection and to make that award. The College in that instance reserves only the right of making no award if a sufficiently meritorious piece of work has not been recommended. We also refer to the Convocational Lectureship, and point out that by tradition the President has the sole responsibility for selecting the Convocational Lecturer. The Committee on Fellowships and Awards believes the James D. Bruce Lectureship and Award could be administered more wisely through a slightly different procedure than either of the above, and recommends the following policies and principles:

"The Fund shall be held by the Treasurer; that part of the income allocated to the Lectureship shall be awarded as a stipend to the lecturer, who shall be appointed annually for each year that the College holds a Session.

"The Board of Regents shall cause to be designed and prepared for the College a medal known as the James D. Bruce Memorial Medal. This shall be presented each year to the lecturer.

"The candidate to receive the award and medal in any year shall be nominated at least four months before the Annual Session of that year by the Committee on Fellowships and Awards. In making the nomination, the Committee may obtain the advice of the Officers, Regents and Governors of the College, and of Fellows appointed by the Committee as referees because of their expert knowledge in the field of Preventive Medicine. The Committee shall obtain the advice of the President; the candidate selected shall be eminent in any of the many divisions of Preventive Medicine.

"The nomination of the candidate shall be approved by the Board of Regents, making it mandatory that the Committee's choice first receive official approval by the President and later by the Board of Regents, or by the Executive Committee of the College.

"The candidate shall deliver a lecture at the Annual Session at which he receives the award. The lecturer shall be described in the program of the meeting as the 'James D. Bruce Memorial Lecturer in Preventive Medicine,' and shall deal with some phase of Preventive Medicine.

"The James D. Bruce Memorial Medal shall be appropriately awarded by the President to the lecturer of the year as a part of the Convocation ceremony. Each lecture shall be published in the ANNALS OF INTERNAL MEDICINE as promptly as possible after its delivery.

"This Fund also had a provision relating to the Alfred Stengel Memorial Award. The Committee has made no final decision on this particular point. The Committee recommends that the cost of preparing the James D. Bruce Memorial Medal be defrayed by the College and not by appropriation from the Fund given by Dr. Bruce.

"The Committee has not made a final selection of a recipient of the John Phillips Memorial Award.

*"Research Fellowship awarded to Dr. Tom Fite Paine, Jr.—*Finally, the Committee recommends that Dr. Tom Fite Paine, Jr., of Boston, be awarded a Research Fellowship, to begin July 1, 1947, in the amount of \$3,000.00."

In the discussion that ensued, Dr. William D. Stroud raised the question as to whether it might not be better to offer, say, three Research Fellowships for a three-year period; that some think there are already too many one-year fellowships, that a man usually just gets started in a year's time, and if he is worth a fellowship, he ought to be allowed at least three years to carry out his proposed investigations. Dr. Waring replied that this had been considered by the Committee. Heretofore in the College it has not been the policy to make extensions of fellowships, that perhaps in view of the fact that there were a great many men coming back from military service, it would be advisable at this time to have more fellowships, rather than an extension of already designated fellowships. The Committee, however, recognizes that a man who undertakes to do research work cannot get very far in just one year, and that perhaps a two-year or three-year fellowship might be desirable—the question being whether this now is the appropriate time for such a change in policy. Furthermore, Dr. Waring expressed the opinion that the present policy does not preclude continuation of a fellowship if the Committee feels that the work in progress is in need of further continuation for completion.

. . . On motion by Dr. William D. Stroud, seconded by Dr. Maurice C. Pincoffs, and carried, the recommendations of the Committee on Fellowships and Awards were approved, and an appropriation of \$20,000.00 was authorized and the report of the Committee accepted. . . .

President Barr pointed out that the Committee on Fellowships and Awards is unprepared to recommend any of the remaining seven possible Research Fellows, and suggested that it would seem expedient this year to give to the Committee authority to choose these fellows and to use its discretion in the amounts which are to be paid each fellow without the necessity of reference to this Board.

. . . On motion by Dr. William D. Stroud, seconded by Dr. LeRoy H. Sloan, and carried, this suggestion was approved. . . .

Dr. Waring, for the information of the Board, offered the following data concerning Dr. Tom Fite Paine, Jr., to whom a fellowship was awarded: age, 28; born, Aberdeen, Miss.; now a Research Fellow, Thorndike Memorial Laboratory, Boston City Hospital; Research Fellow, Department of Medicine, Harvard Medical School; married, has two children; references and teachers—Drs. Hugh J. Morgan and Maxwell Finland; had service in the Army; did hospital work with or under Drs. George R. Minot, William S. McCann and George M. Dack; wishes to work in infectious diseases, with regard to the use of antibiotics under Dr. Maxwell Finland; both Dr. Morgan and Dr. McCann endorsed his excellent record.

The Secretary, Mr. Loveland, asked for directions from the Board concerning the preparation of the James D. Bruce Memorial Medal, its inscription, etc.

. . . On motion by Dr. James E. Paullin, seconded by Dr. William D. Stroud, and carried, the President was directed to appoint a Committee to design a suitable

Medal, and to report back to the Board of Regents at its next meeting, with designs or models for final approval. . . .

(Thereafter, President Barr appointed Doctors George Morris Piersol and O. H. Perry Pepper a Committee of two.)

*Report of the COMMITTEE ON THE ANNALS OF INTERNAL MEDICINE*—Dr. T. Grier Miller, Acting Chairman, in the absence of Dr. Reginald Fitz, Chairman: "The following report was prepared in large part by Dr. Fitz before the meeting of the Committee.

"In May, 1942, Dr. Paul W. Clough was appointed to serve as Acting Editor of the *ANNALS*, to fill the place of Dr. Maurice C. Pincoffs, who had entered military service. He accepted this appointment in troubled times; he faced the possibility of a reduced circulation, dearth of material and financial loss; and then he encountered a shortage of paper, increased costs of printing and irksome delays in the submission of articles for publication and in the delivery by the printer of issues of the journal when finally in press. It was an outstanding achievement to conduct an important medical journal under such conditions, to maintain its literary and scientific integrity, to increase its popularity and to keep it on an even financial keel. The Committee reaffirms its gratitude to Dr. Clough and thanks him again for his loyalty, intrepidity and wisdom.

"When Dr. Clough became Acting Editor, the Board of Regents appointed Dr. W. Halsey Barker, of Baltimore, as Assistant Editor. Dr. Pincoffs has now reopened his desk, and thus the first recommendation of the Committee is threefold: that the Board of Regents welcome the return of Dr. Pincoffs to the *ANNALS*, with satisfaction as well as pride; that Dr. Clough be reappointed Assistant Editor, and that Dr. Barker receive the official thanks of the College for his services by vote of the Board of Regents and in the form of an appropriate personal letter signed by the President.

"The most baffling problem faced by the *ANNALS* at the moment is that of obtaining paper. The Executive Secretary commented on this at the May meeting of the Board of Regents, pointing out the neat decision to be made in determining the quantity of the journal to be printed when, on the one hand, new subscriptions were increasing in unexpected numbers and when, on the other, paper was becoming harder to procure. In June a partial compromise was effected whereby permission was granted to continue the use of the thinner 45 lb. stock paper that had been employed during the War; instead of the more attractive and luxurious 60 lb. paper. Now we are informed by our printers, the Lancaster Press, that the paper situation has not eased and indeed that no means of replenishment of dwindling stocks is immediately in view.

"Though reduced during the War by about 200 pages from its 2700 pages for the year of 1940, a pruning that was artfully accomplished, the Committee believes that still further pruning can be performed without lasting damage to the character and usefulness of the periodical. It now recommends, as emergency and temporary measures, the following:

- (a) that the personal items in the News Notes Section be omitted, thus saving 6%;
- (b) that the Obituary Notices not exceed 300 words, thus accounting for another 1%; and
- (c) that the space devoted to scientific papers be reduced sufficiently to make a total reduction of 10%.

"The Committee approves the salary increases for the Assistant Editor and Secretary, and for the increase in budget to cover honoraria to editorial writers and for other special purposes as submitted to the Committee on Finance by the Editor. It also recommends, in keeping with the current increase in salaries, wages and cost of living, an increase of \$600.00 in the salary of the Editor.



"The Committee asks for acceptance of this report and the adoption of the recommendations contained in it."

... On motion by Dr. Hugh J. Morgan, seconded by Dr. William D. Stroud, and carried, the above report was approved. . . .

*Report of the EDITOR*—Dr. Maurice C. Pincoffs: "The Editor has resumed his duties only for the last four weeks, and certainly feels that the ANNALS has made a great deal of progress in spite of the War. The Regents should thank the Acting Editor for a magnificent piece of work done by a man very heavily burdened with other tasks during the War, and he richly deserves an increase in salary, because of the work he has still to do as the Assistant Editor. At a later meeting I hope to bring before the Regents some thoughts about the future of the ANNALS. It is obvious that we are extending its influence well beyond our membership, and the journal is becoming one of the most widely circulated medical journals in its field, perhaps in the world. It seems to me, although its present policy of make-up obviously has won it that recognition, that responsibility might or should entail some additional contents, some other aspects, since it now returns such a large income. Possibly as an educational feature of the College, it should be expanded."

... The Editor's report was received and recorded. . . .

*Report from the BOARD OF GOVERNORS*—Dr. C. W. Dowden, Chairman: "This meeting of the Board of Regents, midway between the Annual Sessions, means that there is no meeting of the Board of Governors, and, consequently, no deliberations upon which to report. Each Governor was given the opportunity to submit any matter for discussion before this Board, but no problems were submitted. The Board of Governors seems to me to play a very small part in the conduct of the affairs of the College. That is not due to the College; it is not due to the Board of Regents; it is not due to anything except the Governors themselves have failed to set up the proper machinery for obtaining information that might be of great value to the Board of Regents. I think they were very helpful to the Committee on Survey, but aside from that and apart from their endorsing candidates and having representation on the Credentials Committee, they do very little. I am convinced that the Board of Governors could do a tremendous amount of work, and I have been thinking of two or three things: (1) the conduct of State meetings, rather than multi-State Regional Meetings. I don't believe the Board of Governors will ever function as it should when four or five States are put together for Regional Meetings. Those functions are enjoyable, the men enjoy the social side and there are some good speakers, but, after all, I do not think the Multi-State meetings contribute a great deal to the advancement of the College in a personal way in the several States. If the States will each continue to have their own meetings, I believe the plan will attract a far larger percentage of the Governors. For instance, through the War and up to date, Kentucky has been meeting with five or six other States in Chicago; Illinois probably has 80% or 90% attendance of its members, but from Kentucky we may have only 5% or 6%, and, therefore, the meeting doesn't do much good in Kentucky. I would favor an individual Kentucky meeting. In such a case, I could go back from a meeting like this, report on the matters discussed here, we would have a business session, and I could bring back to this Board not only what I think as Governor for Kentucky, but I could tell you what members as a whole of that State are thinking about; that would be a report worth while. I would like to be advised whether such a procedure seems feasible, because it seems to me we are not getting what the membership as a whole would like to have.

"Second, it is becoming more and more evident that the Committee on Nominations must select with great care proper Governors. If the State meetings are resumed, that Committee might well get an expression by secret ballot from the membership of each State on who should be Governor.

"These are just two thoughts which would give the Governors a little more to do, and probably put them in a position to contribute more to the College."

Dr. Maurice C. Pincoffs spoke at length in favor of State meetings, as opposed to multi-State Regional Meetings. He predicted that gradually in various States situations will arise which have already arisen in Maryland, in which the local membership of the College is either trying to abdicate its leadership in Internal Medicine, or is going to have to take on some new responsibilities. He referred to the action of many State medical societies in taking on responsibility of supervision of care of veterans in the office, in the home and in the hospital, by physicians in the State, and said there is inevitably coming up questions as to the qualification of consultants who are paid by the Veterans Administration and whose qualifications are to a certain extent vouched for by the State societies that have taken on, as it were, a contract with the Veterans Administration.

Dr. Pincoffs suggested that the development should be toward some local organization of the College—members being asked by the State society to serve as an advisory committee in helping them to fulfill their responsibility of vouching for certain men as qualified specialists in certain fields—in our case, that of Internal Medicine. He said that if that responsibility is not met and a system of procedure worked out, then we have in a sense abdicated one of our functions in setting up a standard for Internal Medicine. Dr. Pincoffs pointed out that the same thing bears on the relationship of local representatives of the College and the State to such things as consultant care and selection of consultants; more and more there is no question that the medical profession is organizing itself in connection with the movement for medical care of one kind or another; as long as we are in the forefront and the ones who guide it, we shall be meeting a public demand and the effort is sound. Dr. Pincoffs further stated that he thinks the College is going to be called on to play a part, and that part will be at the local level; the stronger the State organization of the College, the better it can take leadership in its field.

Dr. Edward L. Bortz spoke to the question, saying that there has been comment from time to time about the competition between large multi-State Regional Meetings and the regular Annual Sessions of the College, and expressed his entire accord with the comments of Dr. Dowden. Dr. Bortz bespoke an opportunity for younger men in the College to appear on the program of State meetings, thus giving them an opportunity to "win their spurs." He also said that the State meetings would offer a splendid opportunity for the membership of the College to meet likely young doctors who are aspiring to Associateship. Dr. Bortz felt that the program of the State meetings would be of a different character than the large multi-State meetings; that they do not require top flight features and big names, or speakers from long distances.

*Report of the COMMITTEE ON EDUCATIONAL POLICY*—Dr. William S. Middleton, Chairman: "The Committee on Educational Policy starts off with no brief, and has only the future in prospect. Of course on the background of the development of the educational policy of the College, there are certain definite ends that are apparent in the planning of the task. We have, first of all, the annual and regional meetings; the annual sessions have had a certain pattern that apparently arose from the individual initiative of the several successive Presidents. There has been no continuing policy and the Committee yesterday explored the possibility of setting up a program or a council on scientific work, perhaps extending the function of an already existing committee, so that that committee being one in continuity, a standing committee, if you will, could have a projected vision in the organization of the program.

"There was considerable resistance on the part of one member of the Committee, with myself, Dr. Morgan, Dr. Moffatt and Dr. Paullin who attended the Committee meeting. From the present viewpoint, in other words, it did not seem wise that the existing plan of making the President responsible for the program be altered. There was clearly, however, a division, and the two Committeemen there felt strongly that

there might be a change in the allotment of time, so that the annual program might find greater representation in the clinics, panels, the round tables, the clinical and pathological conferences.

"As one goes about the country, as one looks into the organization of successful meetings, he is struck by the fact that the general sessions are ever decreasingly attended and the attention to the clinics and the smaller demonstrations is apparently a growing tendency. I believe that this particular area of development will certainly be explored by the President-Elect, whether it has earlier attention, I do not know, but the Committee on Educational Policy felt that there was certainly a direction of exploration that put an increasing responsibility on the Chairman of Local Arrangements and on the strength of certain of the meetings of the past. For example, here in Philadelphia recently and in St. Louis some years past, the meetings depended upon the strength of the clinical organization. The regional meetings have varied in their representation and effectiveness in considerable measure dependent upon the time, attention and thought given to their development.

"As I have gone over some of the programs, I have investigated the reaction of our attendance upon such programs, and I felt that there was perhaps more strength needed, and it may be that Dr. Bortz's suggestion that the younger men be used has lent itself to their broadening, but has not given as great strength to the older men who were attendant upon them, as we might desire.

"In other words, the Committee as a whole felt that the regional meetings could definitely be strengthened and should be studied with a little bit closer scrutiny by the Committee on Educational Policy. The greatest strength of the past, the greatest contribution to the educational effort, particularly affecting individuals widely spread over the country in the post-war period returning from military service and individuals who were in the period of development from the residency stage to the Associateship and Fellowship, has been in the Postgraduate Courses. I think that there has been no direction of educational effort that has been more widely acclaimed or more generally accepted as a real function of this College. Dr. Bortz deserves particular credit for the organization of these courses and the Committee will hold itself responsible for careful study of that in the future.

"In this direction, Dr. Fitz had written to me from his Committee, asking support of the Research Fellowships. That matter has already been covered and the appropriate grants to strengthen these fellowships have been made available from the College. The Committee on Educational Policy felt it was an unusual source of strength, a proper function of the College, to offer this particular outlet to oncoming men, the leaders of medicine in the future.

"The ANNALS OF INTERNAL MEDICINE has served a very important educational function in the zone of influence of the College and, as pointed out by its Editor, the influence has extended well beyond the membership of the College.

"There was one suggestion that may bear fruit. It has been at least proposed by this Committee that there be offered a sheet, or a page or two, in the ANNALS devoted to significant contributions. The Editor will not necessarily have to list those contributions each month or every two months, or bi-monthly, but he can certainly have the council of members or Fellows of the College in their special fields write as to what they feel in their field has been the outstanding contribution in the period of time given. This is not an effort to start an abstract section, but rather an indication of the trends in medical advances.

"There was one problem placed before the Committee that we did not deem was in our purview, namely, that of establishing a rating function. To be specific, the Memorial Hospital in New York asked that the American College of Physicians give their recognition to certain fellowships that were being established at the hospital. The Committee pointed out that there was only one current rating agency, namely,

the Council on Medical Education and Hospitals of the American Medical Association, and the Committee did not deem it wise for the College to enter into that area."

... On motion by Dr. LeRoy H. Sloan, seconded by Dr. William D. Stroud, and carried, the above report was accepted. . . .

Dr. Morgan requested an expression from the Secretary relative to the directorship of educational activities in the College. Mr. Loveland replied that he felt the educational program was progressing with facility through the coöperation of the Advisory Committee on Postgraduate Courses, the Committee on Fellowships and Awards, the President's Office and the Executive Offices. He referred to the great effort necessary to obtain adequate facilities, faculties and directors to conduct the Postgraduate Courses, pointing out the fact that the College program is conducted on a very much different plan than that for undergraduate and purely review instruction. Dr. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, works in close coöperation and frequent contact with the Executive Offices; directors are selected from among those in whom we have absolute confidence in their ability, insight and wisdom in organizing the proper sort of courses with the proper content and conducted according to the best policies. It would be quite impossible, Mr. Loveland said, to require each of these directors to submit their full programs months in advance, so that they could be surveyed by the Committee on Educational Policy, but all outlines are reviewed by the Chairman of the Postgraduate Committee, and present conditions may eventually change, so that course contents may be obtained longer in advance, in order to have them reviewed by the Committee on Educational Policy. At the present time our directors carry such heavy burdens of teaching and administrative work, and faculties are carrying such a load that it seems unreasonable to demand that they submit their full and detailed outlines many weeks or months in advance of their publication. Mr. Loveland further stated that if the educational program and the Postgraduate Courses are expanded much beyond the present volume, the College may need a man to devote his whole time to work with the Committees on Educational Policy, Postgraduate Courses and on Fellowships and Awards, but under the present program, the College is getting along very well indeed.

*Report of the ADVISORY COMMITTEE ON POSTGRADUATE COURSES*—Dr. Edward L. Bortz, Chairman: "There has been a very definite, marked and spectacular increase in the number of individuals who desire to take the College courses. In 1946 there was an oversubscription in the majority of courses, and a very satisfactory response on the part of those who were asked to organize and direct the courses. There are certain limitations in giving these courses. The load and demands on teaching institutions and teachers who are appropriate individuals as directors of courses are such that we are surprised at the number of acceptances received. Over a period of time one gains experiences that help a great deal in formulating a policy in regard to selecting courses for the future, and contributory to those experiences are the responses from the men who take the courses. For example, one of the valid criticisms has been announcing that an occasional director may use young men who have limited experience and who resort to the literature for outlining their lectures, rather than talking with authority from experience. We have to have teachers of high quality, and the lecture and demonstration must be well prepared before delivery."

Dr. Bortz said the Committee must do the best it can for the present, with regard to one, two or three weeks courses, according to the teachers, material and directors at hand. The Committee had planned about fourteen courses for the spring and an equal number for the autumn of 1947, but probabilities are that this number will have to be somewhat diminished, due to exigencies that may develop. Through the Executive Secretary the Committee is in contact with teachers and faculties of various medical schools throughout the country, and the program is being outlined well in advance. He pointed out that in certain fields, notably Cardiology, there is always wide popular demand. The spring schedule includes courses in: Growth, Isotopes and

Tumor Formation; Cardiovascular Disease; Peripheral Vascular Diseases; Arthritis and Allied Conditions, Internal Medicine. The program will be announced from month to month in the *ANNALS*, and the *Postgraduate Bulletin* published about January 1. The Committee has received splendid support from the Governors and teachers who have given valuable suggestions. The Committee is eager to have any comment from the members of the Board of Regents at any time. Dr. Bortz further said that the matter of collateral reading has been considered some years ago. There was brought up for consideration by this Board the suggestion of publishing under different headings, Cardiovascular Disorders, Gastrointestinal Diseases, Hematology, etc., suggested reading of important new advances described in the literature. The Committee expects there will be some way of working these lists into the *ANNALS OF INTERNAL MEDICINE* from time to time.

*Report of the HOUSE COMMITTEE*—Dr. William D. Stroud, Chairman: "The House Committee, consisting of Dr. William D. Stroud, Chairman, Dr. T. Grier Miller and Dr. Charles L. Brown, with the Executive Secretary, Mr. E. R. Loveland, held a meeting at the College Headquarters on Tuesday, October 1, at 5:30 p.m. Following the Committee meeting, at the direction of the Committee, Mr. George W. Pepper, Jr., Architect, went over in person at the College Headquarters the various items under consideration, and his opinions are added after each item under consideration, as follows:

- "(1) Installation of a door between the private office of Mr. Pindar, Assistant Executive Secretary, and his general office, on the second floor front.

This is an item obviously needed, presents no structural or expensive problems and is recommended.

In this Mr. Pepper concurs and estimates cost at \$200.00."

. . . On motion made by Dr. William D. Stroud, seconded and regularly carried, this recommendation was approved. . . .

- "(2) Installation of a kitchen on the third floor for the caretakers. This would entail covering the floor with linoleum in a room that is already appropriate and available, installing an electric range and a sink.

The caretakers heretofore have utilized the kitchen in the basement, which room is now urgently needed as a machine room for Addressograph, Graphotype, duplicating apparatus, etc.

Mr. Pepper finds no structural problem, considers the proposal practical, and roughly estimated the cost at around \$800.00."

. . . On motion by Dr. William D. Stroud, seconded and regularly carried, this recommendation was approved. . . .

- "(3) The conversion of the present kitchen in the basement to a machine room to house Addressograph machinery, duplicating apparatus and other equipment, thus to relieve the General Office on the first floor.

It is urgently and immediately needed that more space be made available in the General Office for the rapidly expanding files, stenographic staff, etc. The General Office cannot be efficiently administered under the present crowded conditions. Already several of the files have to be kept in the basement, where they are inconveniently located. Such a change would provide temporary relief only. Advantages, however, would arise in moving the noisy machines from the General Office, and providing some additional space for our workers and our files. These machines cannot properly be installed on the Second Floor, because of vibration and noise, nor would they be as convenient to the General Office as in the basement. Further, the operators of these machines are constantly referring to the

files. There is a dumbwaiter already installed between the General Office and the basement."

. . . On motion by Dr. William D. Stroud, seconded and regularly carried, this recommendation was approved. . . .

"(4) The possible installation of a caterer's kitchen in the interior of the basement, providing stove and sink, for use by caterer at Regional Meetings, Board of Regents' Meetings, etc.

Mr. Pepper finds this practical and obviously the only temporary solution to the relief of the General Offices. He points out that perhaps as a temporary measure we might not need to install a caterer's kitchen, but omit for the next year or two any functions requiring a caterer, or obtaining a caterer that can furnish his own warming cabinets."

. . . Dr. William D. Stroud recommended that this arrangement be left to the discretion of the House Committee, and this was approved by the Board. . . .

"(5) Enlargement of the College Building; an extension of the present rear wing to the west about forty feet, which would provide more than double the present space on the First Floor for the General Office and would provide also a large room on the Second Floor for files and clerical staff, or which could be used as a meeting room.

The larger quarters on the first floor have become a necessity. An effective and efficient General Office staff cannot be distributed around small rooms on the second floor, far removed from files and records. Furthermore, second floor rooms are needed for Committee meetings and conferences. The above expansion program would furnish adequate relief, it is estimated, for the next fifteen or twenty years. It would be in keeping with what might then be required for further expansion southward from this additional unit. The College must expect considerable expansion in the next twenty-five years. In the little more than ten years we have occupied the Building, the College activities have multiplied several times. We have an ever-expanding membership, with consequent expansion in files, equipment and staff. The business of taking care of the ANNALS OF INTERNAL MEDICINE alone is a major one, running into some \$70,000.00 a year, the details being made up primarily of \$6.00 and \$7.00 transactions. Mr. Pepper carefully studied this situation and this proposal. He finds no obstacle structurally to match the rear wing of the building, to extend it and to keep it in conformity with the present architecture. He thinks it will in no way detract from the appearance of the building, that it will be practical, not only for the present, but for any necessary extension to the southward in future years to come. He believes that while the work can readily be planned now, construction should be deferred until present building conditions are improved, materials available and costs lower. This will probably be two years hence, but the preliminary work should be planned and completed during the interim, and such authorizations made as necessary.

Mr. Pepper's estimate for the building extension is approximately \$40,000.00. Your Committee does not wish to recommend any appropriation of funds at this time for that extension, but would like authorization to ask Mr. Pepper to draw up plans for it."

. . . Motion of approval was made by Dr. Hugh J. Morgan, seconded by Dr. Maurice C. Pincoffs, and opened for discussion. . . .

Dr. Pincoffs suggested an amendment to the motion to provide that the House

Committee first obtain an estimate for the cost of drawing up the plans by Mr. Pepper. The amendment was accepted by Dr. Morgan, put to vote and carried.

*Report of the CONSULTING COMMITTEE ON ANNUAL SESSIONS*—Dr. David P. Barr, Chairman: "The President has taken seriously the matter of formation of the Annual Session program in Chicago. He has had the advice of many members of the Board of Regents as to subjects and the relative merits of subjects proposed. It is hoped to have a program which is representative of many interests of the College, and a close correlation among the afternoon programs, morning lectures, panel discussions and clinics. The program is still in the formative stage; help and advice are still solicited, particularly help which reflects opinions of Fellows of the College."

Dr. LeRoy H. Sloan, as General Chairman, reported that all clinics in Chicago have been contacted relative to the clinical program, and that the support of all medical schools and hospitals is assured. "Meetings with all the hospitals have been conducted in an effort to extend their vision and understanding of the contents, objectives and the type of attendants. We shall emphasize the basic sciences a little more than heretofore, so as to lift the level of the clinic and not simply to present cases of various kinds. The panel program is well underway. The General Chairman solicits the aid and advice of the Regents and of the Fellows at large in the clinic programs."

*Report of the TREASURER*—Dr. William D. Stroud: "The detailed financial statements of operation for the year 1946 will be presented in connection with the report of the Committee on Finance. You will then see for yourselves that the finances of the College are in very satisfactory condition. A year ago we had anticipated a deficit on the 1946 income, because of our expanded program of Clinical Fellowships, Research Fellowships and the resumption of the Annual Sessions. However, additional income, partially due to the majority of our members returning to civilian work from the Service and active membership in the College, continued growth in Life Membership Fees, increased income from initiation fees, a gift from the late Dr. James D. Bruce, and definitely increased income from the ANNALS, has resulted in our having an estimated surplus in our General Fund of about \$17,000.00.

"Our investment counselors, Drexel & Co., periodically review the College holdings, and the Finance Committee receives monthly statements from the Executive Secretary's Office, thus enabling us to promptly and carefully administer the investment account. On our present invested capital our average yield is now 3.57%, and our investment counselors, in a report just received, estimate the annual income for the coming year at \$13,585.25. The book value of our invested capital is \$364,743.91, and the cash value on October 16, 1946, was \$382,285.75, which shows an appreciation of \$17,541.84."

. . . On motion by Dr. Maurice C. Pincoffs, seconded by Dr. T. Grier Miller, and carried, the report of the Treasurer was accepted. . . .

*Report of the COMMITTEE ON FINANCE*—Dr. Charles T. Stone, Acting Chairman, in the absence of Dr. Charles F. Tenney, Chairman: "The Committee on Finance met yesterday afternoon, October 19, 1946, in the absence of Chairman Charles F. Tenney and Roger I. Lee.

"The following report was compiled with the assistance of Mr. E. R. Loveland, the Executive Secretary, and to some extent with the assistance of President David P. Barr.

"The Committee wishes to report the receipt of a notice from the Probate Court for the County of Washtenaw, State of Michigan, advising that the American College of Physicians has been made a legatee in the will of the late Dr. James D. Bruce.

"The Committee receives and reviews the cash accounts of the College monthly; it is also from time to time canvassed with respect to certain investments and the sale of securities, as occasion arises.

"In accordance with the regulations of the Board of Regents, investments in the Endowment Fund must be approved by the Board as a whole. Since the spring meeting of the Board of Regents, the following security transactions affecting the Endowment Fund have been made:

*Called*

ENDOWMENT FUND		Cost	Called For	Loss
6-27-46	50 Shares, Monsanto Chemical Co., Series 'A', \$4.50, cum. pfd. ....	\$5,878.60	\$5,500.00	\$378.60
6-27-46	4,000 Ohio Public Service, 1st Mort., 4s, due 1962 .....	4,240.75	4,170.00	70.75
				<hr/> \$449.35

*Purchases*

ENDOWMENT FUND		
8-21-46	50 Shares, American Smelting & Refining, 7%, Pfd. ....	\$9,350.00
6- 7-46	5,000 Oregon-Washington Railroad & Nav., 1st, 3s, due 1960 ....	5,300.00
8- 8-46	4,000 Texas & New Orleans Railroad Co., 1st & Refunding, 3½s, Series 'B', due 1970 .....	4,188.60
8-21-46	6,000 Texas & New Orleans Railroad Co., 1st & Refunding, 3½s, Series 'B', due 1970 .....	6,270.00

"For the information of the Board, the following purchases for the General Fund have been made since the last meeting, and are reported herewith for the information of the members:

*Purchases*

GENERAL FUND		
6- 7-46	200 Shares, Commonwealth & Edison Corp., common .....	\$7,218.24
6- 7-46	5,000 Oregon-Washington Railroad & Nav., 1st, 3s, due 1960 ....	5,300.00
6-12-46	100 Shares, Philadelphia Electric Co., common .....	2,962.50

"These purchases have in all instances been made upon the recommendation of the investment counselors. The Finance Committee receives periodically analyses of all College security holdings; the last was under the date of October 16, 1946, in which communication Drexel & Co., the investment counselors, recommended no changes in the present portfolio. It was recommended that \$2,217.00 in cash available in the Endowment Fund be used to purchase 50 Shares of Pacific Gas and Electric Co., 6%, preferred stock, currently selling at about 40¼, to yield about 3.73%."

... On motion, seconded and regularly carried, this portion of the report was approved. ...

"For some years past, the College has maintained a bank depository in the Dominion of Canada. The total amount of the deposit at present is \$8,954.53. Drexel & Co. suggests, and we recommend, that \$7,000.00 of this amount be transferred to our Philadelphia depository."

... On motion, seconded and carried, this portion of the report was approved. ...

"When the last annual budget was prepared there was no knowledge that the College would receive the gift of \$10,000.00 from the late Dr. James D. Bruce, which was announced at the spring meeting. This has been set up as the Bruce Fund, in accordance with directions of the Board of Regents. The fund has been invested in full in U. S. War Savings Bonds, 2½s, Series 'G', due March 1, 1957. The income of \$250.00 per annum will be divided into halves, the first half for the founding of a



memorial award to the late Dr. Alfred Stengel and the other half allocated to an annual lectureship or award in the field of Preventive Medicine.

"When the budgets for 1946 were authorized it was anticipated that expenditures would exceed receipts by approximately \$25,000.00. Actually the total income for 1946, based on actual figures for the first nine months and estimates for the last three months, indicate that there will be a surplus of approximately \$54,000.00. This is not a true surplus, in that slightly over \$25,000.00 received from Life Membership Fees and the Bruce gift go into the Endowment account and current outstanding obligations on fellowships of a little over \$11,000.00 reduces the balance to approximately \$17,000.00. In addition to the amounts received from Life Membership Fees and the Bruce gift, larger amounts than anticipated were derived from subscriptions to and advertising in the *ANNALS OF INTERNAL MEDICINE*.

"The Committee has studied the budget for 1946 and finds that the College has operated at less than budget appropriations in all departments except the College Headquarters, with a deficit of \$59.56, and the *ANNALS* budget for the Executive Secretary's Office, with a deficit of \$8,923.24, due to the big increase in the expansion of the *ANNALS* and in the cost of printing the journal. As a whole, the College operated at \$19,628.57 below total budget appropriations.

"An estimate of income and expenditures for the year 1947 gives the following totals:

Estimated Total Income .....	\$158,700.00
Estimated Total Expenditures .....	153,296.61
	<hr/>
Balance .....	\$5,403.39

"In the budget for the President's Office for the Twenty-eighth Annual Session, the Committee, after conference with President Barr, recommends that the amount allocated to traveling expenses, including guest speakers, be increased from \$1,000.00 to \$1,500.00.

"The Committee recommends that the salary of Mr. F. V. L. Pindar be increased from \$5,500.00 to \$6,000.00 per annum, effective July 1, 1947, in accordance with agreement at time of appointment.

"The Committee further recommends the adoption of the Budget for 1947 as a whole."

... On motion, seconded and carried, this portion of the report, including the adoption of budgets, with any additions specifically voted at this meeting, was approved. ...

*"College Dues*—Fellowship dues were \$20.00 and Associateship dues were \$15.00, up to the end of 1932. At that time they were reduced from \$20.00 to \$15.00, and \$15.00 to \$12.00, respectively (\$10.00 to full-time teachers, military officers, research workers, etc.). Everything costs materially more now; the College services and activities have been tremendously increased; the journal costs at least 35% more to publish, and the College cannot continue the desired expansions without increased dues.

"The present dues are considerably less than a number of other societies, such as the American College of Surgeons, the American College of Radiologists and others. We have been informed that the American College of Radiologists will increase their dues, if not already, to \$50.00 per annum. We do not know whether the American College of Surgeons will increase its dues or not, but they have never been below \$25.00 per annum. State medical societies have in approximately 50% of the cases increased their dues recently, the dues varying from \$5.00 per annum up to \$100.00 per annum. Furthermore, additional funds might well be used partially toward the proposed Building Fund for enlargement of the College Headquarters, which has been discussed by the House Committee. Many members feel our dues are exceptionally

low for the services we perform, and a return to dues of \$20.00 and \$15.00 for Fellows and Associates, respectively, and an increase to \$12.00 for full-time teachers, military officers, etc., would meet, we believe, with the approval of the members at large. The Board of Regents has authority under the By-Laws."

. . . On motion by Dr. Maurice C. Pincoffs, seconded and carried, this portion of the report referring to dues was approved. . . .

"Interpretation of present regulations concerning fees of Medical Officers—When present regulations governing fees were adopted many years ago, members of the Medical Corps of the Army, Navy and Public Health Service were accorded fees under Class D—initiation fee, \$10.00; annual dues, \$10.00. At that time few, if any, Medical Officers received salaries adequate to enable them to pay the ordinary fees. The regulations, however, state 'included also in Classes B, C and D are members of the Medical Corps of the Army, Navy and Public Health Service.' A strict interpretation of this would mean that if a Medical Officer receives a salary of \$5,000.00 or more per annum, he should pay an initiation fee of \$50.00 and dues of \$10.00; if his salary is less than \$5,000.00, an initiation fee of \$25.00 and dues of \$10.00. To date, however, Class D has been reserved wholly for Medical Officers, and none of them has paid an initiation fee of more than \$10.00. The question is whether this needs reinterpretation, or that we shall continue under the old precedent. This is submitted to the Board of Regents for discussion without recommendation."

. . . On motion by Dr. Maurice C. Pincoffs, seconded by Dr. Hugh J. Morgan, and carried, it was

RESOLVED, that the fees of Medical Officers remain as heretofore, due to the fact that the number of individuals affected is extremely small. . . .

. . . On motion by Dr. Charles T. Stone, of the Finance Committee, seconded by Dr. Hugh J. Morgan, and regularly carried, an honorarium of \$100.00 was appropriated for the Secretary to the Treasurer, in consideration of her work for the College (1946 Budget). . . .

President Barr pointed out that the Budget as prepared and approved did not include certain items which were acted on at this meeting, as follows:

\$ 500.00 additional, President's Budget  
8,000.00 additional, Committee on Fellowships and Awards  
600.00 increase in Salaries, Editor's Budget  
600.00 (1946), House Committee

These additional appropriations would wipe out the anticipated surplus on the budget prepared by the Executive Secretary, but on the other hand, the increase in dues will restore a small surplus.

Dr. James J. Waring brought up the matter of the traveling expenses for the Convocational Lecturer, the James D. Bruce Medalist and the John Phillips Medalist, and, after discussion, a resolution was regularly adopted providing that the traveling expenses of the Bruce Medalist be paid by the College. Precedent had already been set by which the College paid the traveling expenses of the Phillips Medalist and also of the Convocational Lecturer, where said lecturer is a non-member of the College.

President Barr brought up for discussion the matter of allowances made to Officers and Regents of the College for expenses when traveling on official College business, saying the regulations for the past many years has been that such expenses be limited to \$5.00 per day in transit and \$10.00 per day in residence, an amount which is now entirely inadequate to cover expenses. These same allowances are made to invited guests on the program of the Annual Sessions who are non-members of the College.

... On motion by Dr. Hugh J. Morgan, seconded by Dr. Maurice C. Pincoffs, and carried, it was

RESOLVED, that the traveling allowances be increased to \$7.50 per day in transit and \$15.00 per day in residence. This does not affect the regulations which also provide for payment of first-class round trip train and pullman fares, nor does it apply to Officers and Regents attending the Annual Sessions of the College.

*Report of the AMERICAN BOARD OF INTERNAL MEDICINE*—Dr. James J. Waring, Chairman: Dr. Waring had no formal report, but referred again to the preceptorship type of training for credit toward admission to Board examinations. Between this date and July 1, 1947, when preceptorships will terminate, Dr. Waring expressed the hope that some arrangements can be effected to reconcile all the differences of opinion and to make available resident or non-resident training that will satisfy everyone.

Dr. William D. Stroud inquired what method should be followed by a young man who is starting in hospital graduate training who wants not only to qualify for certification, but also for membership in the College. Dr. Stroud especially wanted to know how to obviate the situation whereby the young man might follow a plan approved by the American Board of Internal Medicine, which might not be approved by the Committee on Credentials.

President Barr replied that one of the purposes of the Survey Committee was to coördinate certain of these requirements between the American Board of Internal Medicine and the American College of Physicians, but said that this matter is entirely within the discretion of the American Board of Internal Medicine and the Credentials Committee of the College, and at present there are no rules that can be predicted.

Dr. Charles T. Stone commented that in his opinion it is unlikely that either the American Board or the College would take exception to residency training approved by the Council on Medical Education and Hospitals of the American Medical Association, which is the only accrediting agency for setting up and approving residencies for training. Furthermore, it was pointed out that both the American College of Physicians and the American Board of Internal Medicine have conference committees which work with the Council.

President Barr reminded the Board that the American College of Physicians appointed a representative to, and appropriated \$1,000.00 for, the Council for Study, Prevention and Treatment of Rheumatic Fever, and asked for a report.

Dr. Stroud said that the Council has started a study of 10% of the 40,000 members of the Armed Forces that had rheumatic fever and are selecting a certain group with the help of the Veterans Administration in various parts of the country. Boards will be set up to examine these individuals, to determine if they had rheumatic fever and what their cardiac status is. There will be another 4,000 as a control group in the same towns, coming from the same boards. The study will cost about \$500,000.00, which has been donated by an interested lady. Dr. Stroud further stated that the American Council on Rheumatic Fever now hopes the College will turn over its appropriated \$1,000.00 for use in starting a national registry in the office of the American Heart Association. The money will be used for printing questionnaires and obtaining their return. In this manner it will be possible to learn just what the rheumatic fever and rheumatic heart problem is in this country.

President Barr announced that the next meeting of the Committee on Credentials will be held in Philadelphia, March 30, 1947, and the next meeting of the Board of Regents will be held at the Palmer House, Chicago, April 27, 1947.

Adjournment.

Attest: E. R. LOVELAND,  
Secretary

## OBITUARIES

## DR. CLYDE MULHOLLON FISH

Thursday morning November 21, 1946, Dr. Clyde Mulhollon Fish, age seventy-one years, died of cerebral hemorrhage in the Atlantic City Hospital and was laid to rest in the town of his birth, Bath, Pa.

He was a student at Lehigh University and Rush Medical College in Chicago. He received his degree upon graduating from Jefferson Medical College in 1897. He served his internship in the Atlantic City Hospital and then followed a few years as an associate to Dr. B. C. Pennington at Atlantic City.

He then took up his residence in nearby Pleasantville, N. J. As his reputation as a diagnostician spread, his clientele came from all over South Jersey.

Dr. Fish was Superintendent of the Atlantic County Hospital for Tuberculosis until 1925 and Medical Director from 1941 until the time of his death. He became Director of the Tuberculosis League in 1919.

Dr. Fish became a Fellow of the American College of Physicians in 1930. He was a Mason, with membership in several Masonic organizations. He was a member and active in the following scientific organizations: American Federation of Sanitaria; National Tuberculosis Association; Aesculapius Club; The Medical Society of New Jersey; Past President of the Medical Society of Atlantic County; Atlantic City Academy of Medicine and the New Jersey State Tuberculosis League. He was active in the Kiwanis International.

Dr. Fish earned an excellent reputation as an internist and as an authority on tuberculosis. He was a very modest man; indeed, he was so modest and humble that he himself never realized his surprising ability and with modesty and humbleness he possessed the virtue of kindliness.

DAVID WARD SCANLAN, M.D., F.A.C.P.

## DR. SYDNEY PEYSTER WAUD

Dr. Sydney Peyster Waud (associate), Chicago, Ill., died unexpectedly on October 19, 1946.

Dr. Waud was born August 23, 1909, in Oak Park, Illinois. He attended Princeton University from 1927 to 1931, following which he entered the Medical School at Northwestern University, from which he was graduated in 1934. Following an internship at the Presbyterian Hospital in Chicago, he did some post graduate work at Cook County Hospital. He practiced internal medicine in Chicago from 1936 to 1940. He was commissioned in M.C., A.U.S., in November of 1940, where he served with distinction until he was discharged in April, 1946, with the rank of Colonel. During his service, much of his time was spent overseas, the last two years

being spent in India. While serving in India, he developed a great interest in tropical medicine as well as in other infectious diseases which continued after his return to civilian practice. Following his discharge from service, Dr. Waud entered private practice in Chicago.

He was Clinical Assistant in Medicine at Northwestern University Medical School; Attending Physician, Veterans Administration Hospital, Hines, Illinois; and he was on the staff of the Passavant Hospital. He was a member of the Chicago Medical Society, Illinois State Medical Society, and the American Medical Association. He was also a member of the Chicago Heart Association, Association of Military Surgeons, and was an Associate of the American College of Physicians. He was the author of several published articles on various medical subjects.

Dr. Waud possessed a remarkable physical stature, and his sudden death at the age of 37 was a great surprise. He possessed great physical energy, and with this he coupled an unbounded enthusiasm and friendly good fellowship which he radiated both to patients and fellow workers. All who knew him believe that death has interrupted a promising professional career. His loss is sincerely felt by patients and associates alike.

LYLE A. BAKER, M.D., F.A.C.P.

### DR. HARRISON AYER CHASE

Dr. Harrison Ayer Chase, F.A.C.P., Falmouth, Massachusetts; born in Brockton, Massachusetts; December 11, 1877. Ph.B., 1901, Brown University; M.D., 1905, Harvard Medical School; intern, 1905-1907, Staten Island Hospital; postgraduate work, Harvard Medical School and New York Post-Graduate Medical School and Hospital; on the staff of the Goddard Hospital, Brockton, Massachusetts since 1909, having served in many capacities, including Physician-in-Chief; served at one time as Secretary, Vice-President, and President of the Brockton Medical Society. Member, Massachusetts Medical Society and American Medical Association; Fellow of the American College of Physicians since 1931; Diplomate, American Board of Internal Medicine; Director, Child Clinic, Brockton Visiting Nurses Association.

For many years Dr. Chase practiced both obstetrics and internal medicine. His chief interest over the years was obstetrics. He followed each new development with keen interest and its worth had to be proved to his satisfaction before it was adopted in his clinic.

Harrison Ayer Chase was a man of deep integrity, simple in his tastes, reserved yet deeply sympathetic and humane. He leaves a far reaching influence upon the community he loved and served for many years.

CHESTER S. KEEFER, M.D., F.A.C.P.,  
Governor for Massachusetts

# ANNALS OF INTERNAL MEDICINE

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## MEDICINE IN THE EUROPEAN THEATER OF OPERATIONS \*

By WILLIAM S. MIDDLETON, F.A.C.P., *Madison, Wisconsin*

THE Professional Services Division of the Chief Surgeon's Office in the European Theater of Operations did not spring into functional maturity upon the declaration of war by the German Reich. A comprehensive plan of consultation service had been projected in the American Expeditionary Forces in World War I. Armistice came before all of its weaknesses had been remedied. In World War II a group of distinguished specialists constituted the Army Medical Directorate Consultants' Committee to the Director General of the Royal Army Medical Corps in London, whereas two able clinicians and a pathologist acted as professional advisers to the Director General of the Royal Canadian Army Medical Corps. With these experiences ready at hand the basic plan for medical supervision of the American forces in the European Theater was early adopted; nor was it materially altered in the three years of operations.

On the staff of the Chief Surgeon and administratively next in responsibility for the medical care of the sick and wounded was the Director of Professional Services. Under him were the Chief Consultant in Medicine and the Chief Consultant in Surgery. Turning immediately to the Medical Consultation Service (figure 1), Senior Consultants in the medical subspecialties carried the continuity of responsibility. Neuropsychiatry, dermatology, infectious diseases, cardiology and tuberculosis were here represented. Neuropsychiatry is a heavy service in military medicine. With the delegation of the care of venereal diseases to medicine, dermatology assumed the supervision of this added clinical load and became a close runner-up to neuropsychiatry. Hence, the Senior Consultants in Neuropsychiatry and

\* Presented at the 27th Annual Session, American College of Physicians, Philadelphia, May 13, 1946.

From the Department of Medicine, University of Wisconsin Medical School.

The figures herein quoted were graciously afforded by Col. Joseph H. McNinch, Director of the Historical Division, Surgeon General's Office. They are still tentative. Col. John E. Gordon, Chief of Preventive Medicine Division, Chief Surgeon's Office, European Theater of Operations, gave further invaluable data.

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Dermatology, with full-time tasks, were stationed at Headquarters. The Senior Consultants in Infectious Diseases, Cardiology and Tuberculosis, on the other hand, were primarily concerned with policy formation in their restricted areas of medical activity. They were selected from qualified chiefs of the medical services of fixed hospitals and continued to act in the dual capacity of chief of the service and Senior Consultant to the Theater in the medical subspecialty. With the growth of the Theater these Senior Consultants were severally advanced to the status of Regional Consultants and then to Base Section Consultants. They still retained their subsidiary, but

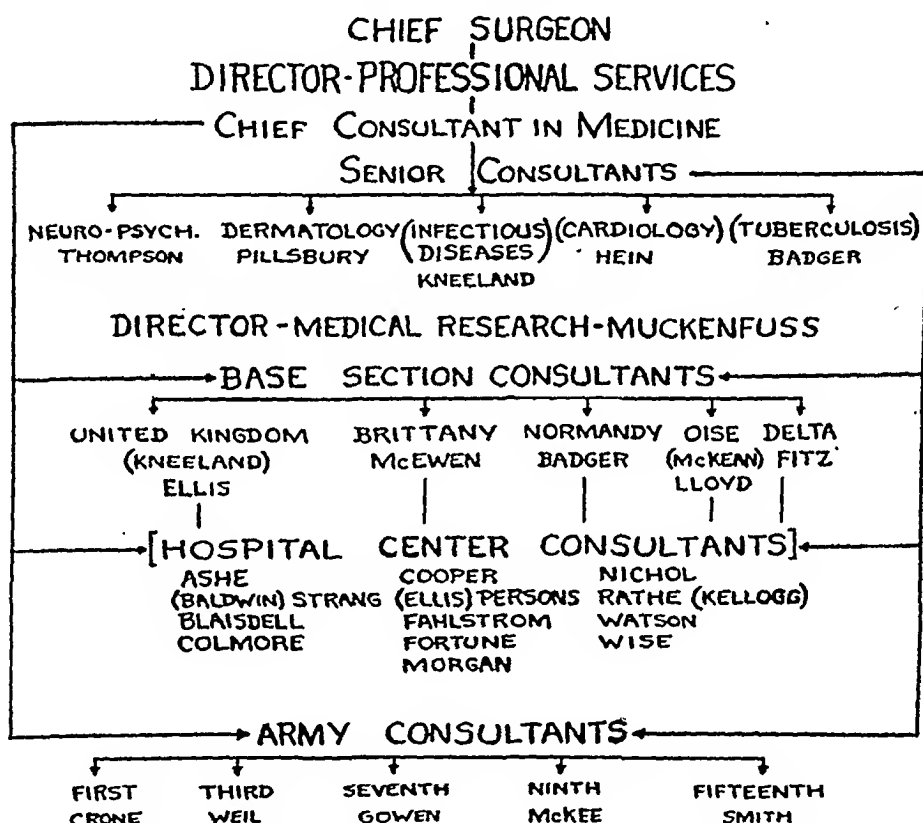


FIG. 1. Plan of organization—Medical consultation service in the European theater of operations.

important, rôle of advisers to the Theater in their respective spheres. Additional Base Section Consultants were required. In a few instances their tasks were so onerous as to preclude further clinical duties; but where there was a restricted area of activities, a qualified chief of a medical service was selected. With the evolution of hospital center program, appropriate leaders were selected from among the chiefs of the medical services of the component units to act in a second capacity as Medical Consultant to the group. Instead of over 200 scattered units, from a professional as well as an administrative standpoint, prompt contact could be made at 15 points of command (seven hospital centers in the United Kingdom, eight on the Continent).

The Medical Consultants in the Armies (five) constituted the ultimate link in the continuity of professional communication. Through these Army consultants medical policies were implemented in combat elements and a unity of medical approach assured through all echelons.

Although research is not a primary function of the Medical Department in the active Theater of Operations, it was deemed expedient to organize the continuing flow of medical information and clinical inquiry in a central office. Accordingly, the post of Director of Medical Research was established to coordinate such efforts. A file of research projects was maintained. All proposals requiring financial support or the transfer of personnel were investigated and their merit rated upon the grounds of military bearing, solubility in a short time and availability of the necessary materials and personnel. Upon such advice the Chief Surgeon could then act with clear insight. The Director of Medical Research continued in his primary responsibility as Commanding Officer of the 1st Medical General Laboratory.

In the schematic outline of the Medical Consultation Service in European Theater channels of professional communication have been drawn. Official channels were used in all matters relating to military or tactical procedure; but with the support of the Chief Surgeon, Major General Paul R. Hawley, direct communication in purely professional details was encouraged. By this expedient, operating through the simplified system of decentralized control, information regarding disease trends, therapeutic innovations and similar medical data might be promptly disseminated. Nor was the advantage unilateral; frequently the initiating source of valuable information was an isolated field unit or mobile hospital. The Chief Consultant in Medicine held periodic Conferences of the Chiefs of Medical Services. This important integrating agency was later decentralized to Base and Hospital Center levels. Monthly meetings of the Professional Services Division under the Chief Surgeon supplemented weekly informal gatherings of the Consultants at Headquarters. To these sessions all Senior Consultants and Base Section Consultants were invited.

The Medical Consultation Service sought to offer the highest possible medical service to every American soldier. Perhaps the most important element in rendering such a service effective was the confidence of the Chief Surgeon in its mission. Under his leadership the Professional Services Division became the focal point of the Medical Department in the European Theater. The closest rapport existed between the Medical Consultation Service and the Preventive Medicine Division of the Chief Surgeon's Office. The propinquity and the interlocking interests of these elements rendered immediate intelligence in all matters pertaining to the health of the command possible. Their functions must always be interdependent. The Senior Consultant in Infectious Diseases, the Chief of Laboratories and the Chief of the Preventive Medicine Division constituted the Advisory Committee on Infectious Diseases which coordinated the mutual effort in that area.



Obviously to insure the best medical service under all conditions there must be the optimal utilization of the available personnel. All new hospitals assigned to the Zone of Communications were visited upon arrival in the Theater. By personal interviews and staff conferences evaluations of the unit as a whole and of its component members were made. (In 1944 the Chief Consultant in Medicine personally visited and interviewed the officers of the Medical Sections of 108 general and 11 station hospitals from the Zone of Interior and four general and two station hospitals from MTOUSA.) Marked discrepancies in numbers and qualifications became apparent as the reserve of medical officers in the United States was exhausted. Fortunately the affiliated hospitals that had first arrived in the Theater and those transferred from MTOUSA afforded a wealth of qualified and tried internists. From this reservoir 58 new chiefs of medical services were made; but the dilution was becoming precarious by 1945. On the other hand tours of duty in the Armies disclosed occasional instances of inadequately utilized skills. On the initiation of the Army Surgeon, the consultant would make the recommendation for appropriate exchange. The Personnel Division depended implicitly upon the Professional Services Division for advice in these directions. To their everlasting credit it should be stated that never was a recommendation for the movement of a medical officer in the interest of better care for the soldier made by the Medical Consultants without prompt compliance.

Although more directly involved in matters relating to personnel than certain other functions of the Chief Surgeon's Office the consultants were apprised of the tactical situation. The Finance and Supply Division advised with Professional Services upon drugs, supplies and equipment dealing with the immediate care of patients. In accepting drugs of foreign origin the Chief Consultant in Medicine conferred with British representatives to establish standards of equivalence. The counsel of the consultants was sought in arranging Tables of Basic Allowance for chemicals and drugs for all operations. Policies of hospitalization, evacuation and redeployment were established after conference with the affected consultant. All directives for therapy emanated from this Division.

The interest of the Medical Consultants was fundamentally clinical. In the early days of the Theater the Chief Consultant in Medicine made monthly clinical rounds in each hospital in the United Kingdom. This recurring contact with the practice of the area gave an excellent opportunity for co-ordination and ultimately paid unanticipated dividends in a knowledge of the most promising young clinicians who were later required to strengthen medical services in the understaffed new units. With the ever increasing troop lift and hospitalization program (total beds 259,725, of which 183,550 were in fixed hospitals) the ideal of monthly clinical rounds was met by decentralization. Instead of a single individual for the Theater, a Base Section or a Hospital Center Consultant made periodic professional visits in the area of his responsibility.

For the advancement of medical service the several reports to the Medical Records Office were made available to the Consultants. Aside from the indication of the immediate disease incidence probably their most useful purpose was met in the Weekly Statistical Reports of deaths. The occurrence of preventable disease in these weekly lists was checked by direct correspondence with the chief of the medical service in the hospital reporting the death. From him the complete clinical record was obtained. Thereupon a duplicate set of the histologic sections was reviewed and all points of discrepancy reconciled. With this evidence in hand the situation was reconstructed. Then an analysis with criticism and advice was forwarded to the responsible medical chief. Naturally it is impossible to evaluate the profit of such a course of procedure; but there were dividends in improved care of the sick.

The educational program was close to the heart of the Professional Services Division. The routine hospital staff meetings were supplemented by the ETO Medical Society which met periodically in one of the general hospitals. With the growth of the Theater, it was supplanted by regional meetings. Broadening in their influence were the Inter Allied Conferences in War Medicine held in the Royal Society of Medicine under the chairmanship of Sir Henry L. Tidy. The Inter Allied Consultants' Conferences afforded an excellent, but infrequent, medium of interchange. The Operations and Training Division of the Chief Surgeon's Office organized the Army Medical Field Service School at Shrivenham, England, and later at Chateau du Marais, near Etampes, France for the conduct of courses in field medicine and surgery. In a similar vein the 8th Air Force developed the 8th Air Force Provisional Field Service School at High Wycombe, England. With the cessation of hostilities, several ambitious educational programs were initiated by the Training Branch of the Operations Division. Clinical exposures at general practice and specialty levels were evolved in hospital centers. With the coöperation of leaders in internal medicine in Great Britain a splendid preceptorial plan was instituted. Many of the details of these well conceived patterns of training disintegrated with the rapid redeployment in the Summer of 1945.

In 1942 temporary exchanges of medical officers of company grade were arranged between the 5th General Hospital and tactical units in training in North Ireland. The anticipated bilateral advantage was generally acclaimed and warranted its much wider application in the interest of professional advancement and medical care. Apparently unjustified obstacles were placed in the way of its more regular and adequate implementation. For the medical officers of the 8th Air Force periods of observation were arranged in fixed hospitals. Both of these plans gained momentum in the Spring of 1945. In a further endeavor to bring the clinical aspect of the field into sharper focus, a medical follow-up card was prepared. The interested medical officer, transferring a sick soldier from a tactical or detached unit, was merely required to write his own name, unit and APO on

the front of the card and the soldier's name on the reverse side. The first medical officer, giving definitive care to the soldier, would supply the brief salient information as to subsequent course, diagnosis, treatment and disposition. Thereupon by post the card would be returned to the initiating medical officer.

The European phase of World War II was a surgical war. We escaped serious epidemics, and hospital admissions for trauma exceeded those for disease for the first time in military history. Beyond a peradventure, measures of prevention must be given full credit for this amazing record. If a single disease, typhoid fever, notorious as an index of the filth of a campaigning Army, be taken as a guide, we find a most arresting situation (table 1). In four years there were 46 instances of typhoid fever in the

TABLE I  
Typhoid Fever  
European Theater of Operations, U. S. Army  
Cases and rate per 1000 strength per annum, by month and year  
February 1942-June 1945 Inclusive

Month	Total	1942	1943	1944	1945
January	4	—	—	3	1
February	1	—	—	—	1
March	6	1	—	—	5
April	3	—	—	—	3
May	3	—	—	—	3
June	8	—	—	—	8
July	—	—	—	—	—
August	—	—	—	—	—
September	4	—	—	4	—
October	—	—	—	—	—
November	13	—	—	13	—
December	4	—	1	3	—
Total	46	1	1	23	21
Rate	.014	.014	.004	.009	.015

Source: Division of Preventive Medicine, Office of the Chief Surgeon, ETOUSA.

American forces in the European Theater of Operations, with two deaths. Living under the variable sanitary conditions of the field, an Army of over three million had a typhoid rate of 0.014 per thousand strength per year, a remarkable tribute to sanitation and typhoid vaccination. The figures for dysentery are somewhat less convincing and they apply only to the period between February 1944 and June 1945, as follows:

	Admissions	Rate/1000
Bacillary dysentery	1,054	0.4
Amebic dysentery	780	0.3
Unclassified dysentery	1,435	0.5

As predicted on many hands the availability of sulfonamides, active in the control of bacillary dysentery, materially reduced the morbidity from this

disease. By the same token the etiologic definition was even less exact than in World War I. Both prophylactically and therapeutically sulfadiazine proved most efficacious. Although there can be little doubt of the occurrence of viral dysentery (Reimann), considerable confusion was interposed by the regular use of sulfonamides in these patients, with or without the benefit of medical advice.

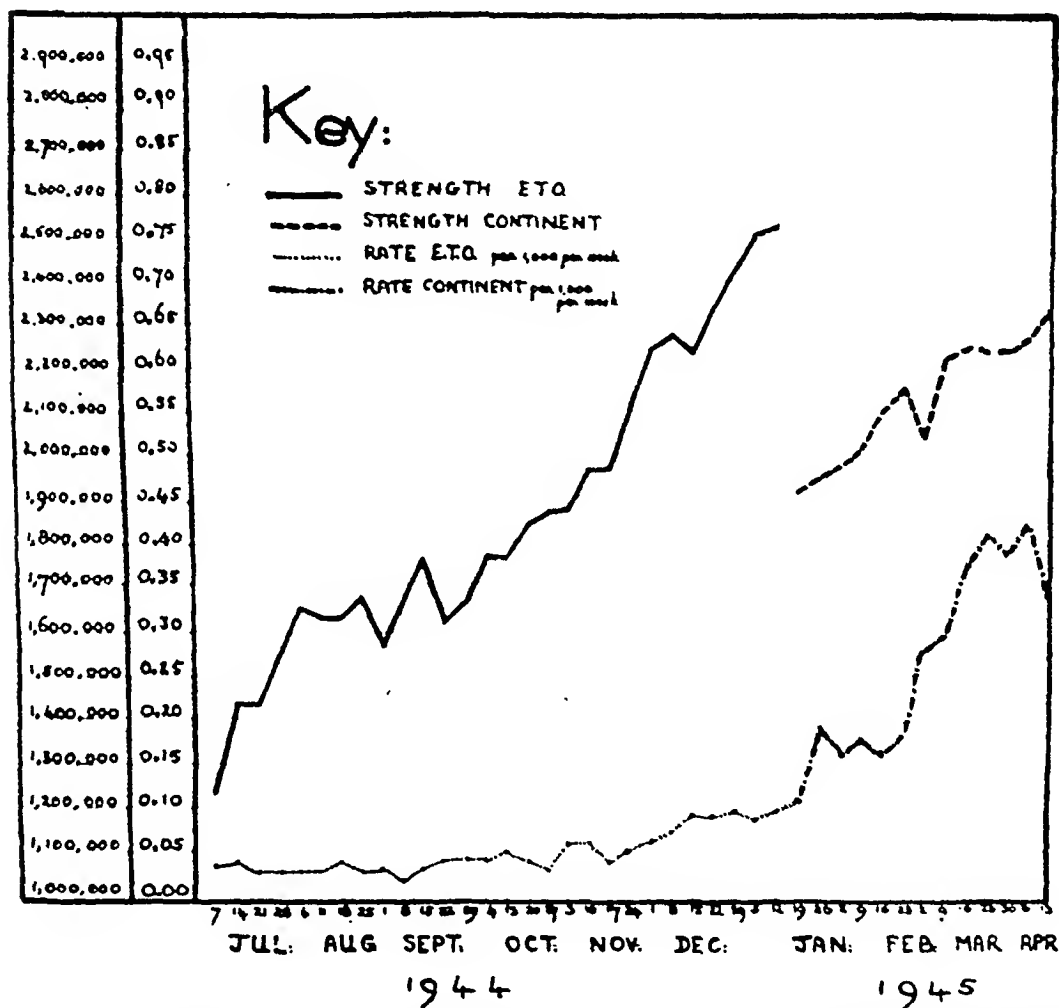


FIG. 2. Infectious hepatitis. The break in the curves of troop strength and disease incidence is necessitated by the availability of records. It will be noted that after the week of January 19, the curves relate to the continent only.

Viral hepatitis constituted a problem of some magnitude in the European Theater. Beginning with the heavy charge of postvaccinal jaundice (yellow fever) in 1942, the naturally occurring hepatitis and homologous serum jaundice were continuously encountered. A total of 22,223 instances was met—an annual rate/1000 strength of 6.99. The curve of incidence (figure 2) found the peak of 952 admissions for hepatitis the week of April 6, 1945. The total number of deaths was 68 (0.3 per cent). In a limited survey of

homologous serum jaundice in this Theater, Kneeland reported 14 deaths among 146 (9.5 per cent). Such experiences multiplied in the several theaters of operations and in the civilian field will unquestionably influence medical thought and practice in the prophylaxis of this preventable type of hepatitis. From a clinical standpoint the remarkable recuperability of the liver was reestablished; the tests of hepatic function had a limited usefulness; rest and high protein, high carbohydrate, low fat diet with vitamin B<sub>2</sub> supplements were the chief directions of therapeutic attack. A well controlled study in the 121st Station Hospital established no especial advantage of the sulfhydryls over high protein diets. Concurring in the general experience rest was an essential to the most prompt and adequate convalescence. Deferment of rest prolonged the course of viral hepatitis and premature effort usually led to relapses.

Respiratory infections were a lesser source of manpower attrition in Great Britain and Europe than anticipated. In general the curves of incidence were lower in the European Theater than in the Zone of Interior. In the Fall of 1942 primary atypical (viral) pneumonia occurred in great numbers, but it never reached epidemic proportions. Important, however, was its preponderance over bacterial pneumonia through the period of the war (19,477 compared with 12,046). The mortality for primary atypical (virus) pneumonia was 0.2 per cent and for bacterial pneumonia 0.53 per cent. No therapeutic advances were recorded in viral pneumonia. In pneumococcal pneumonia penicillin clearly took priority over the sulfonamides. In November, 1943 virus A influenza made its appearance in an explosive epidemic. It was singularly free from complications and mortality. Had it been the primary wave of a pandemic, the secondary wave would have coincided with the invasion of Normandy!

Meningococcal infections bade fair to be a formidable problem in Europe. Actually there were only 2,138 instances. As compared with the mortality of 38 per cent in World War I, the figure fell from 5.3 per cent in 1942 to 2.8 per cent in 1944. Such improvement arose from early diagnosis and more effective therapy. Sulfadiazine, parenterally and orally, and penicillin, intramuscularly and intrathecally, were stout allies. Antimeningococcus serum was not employed in any degree. Sulfadiazine won its spurs in the chemoprophylaxis of this disease.

From secret sources a high incidence of virulent diphtheria was reported in the Low Countries and Scandinavia before D-Day. On this basis a greatly augmented supply of antitoxin was carried into Europe by our forces. Diphtheria was not an early problem; but soon its occurrence and gravity among German prisoners of war caused concern. At one time in a single camp of 20,000 of these prisoners there was more clinical diphtheria than in the entire United States Army in Europe. Epidemiologists attempted to explain this divergence upon the spacing of immunes in our forces. With increased civilian contacts, however, the disease appeared with increasing

frequency among our troops. In all 1,377 instances were diagnosed; but late complications occurred entirely too frequently. Too much dependence upon the laboratory deferred or obscured the diagnosis. A mortality of 2.3 per cent marred the record.

Typhus fever became a problem after crossing the Rhine. With DDT and the protective vaccination it was never a serious threat to the health of the command. In all, 21 American soldiers suffered from this disease. Where the immune barriers were breached, the disease found expression in a much milder form. None of them died. Malaria appeared largely as a legacy from the Mediterranean area. Most frequently it was the relapsing form of benign tertian malaria. At times clinical manifestations developed for the first time in soldiers parasitized elsewhere. Atrabine discipline was a fluid factor in spite of strong representations and directives. A total of 24,751 victims (or an annual rate/1000 strength of 7.78) was reported. Among these, six (0.02 per cent) died.

From the standpoint of prophylaxis the record for tetanus is unparalleled among the infectious diseases. In the American troops of the European Theater protected by tetanus toxoid followed by a booster dose upon trauma, an isolated instance of tetanus developed. This patient died. Among the German troops only the Luftwaffe and certain paratroop elements received prophylactic vaccination. The remaining unprotected German prisoners of war afforded a horrible control in their high morbidity and mortality from tetanus.

So careful was the screening of inductees that cardiovascular problems were at a minimum. Precocious coronary occlusion arrested passing attention. Rheumatic fever was less frequent than anticipated. Mediastinal trauma gave an unusual opportunity for its electrocardiographic study at the 160th General Hospital. Mass radiography paid fine dividends in the extremely low incidence of tuberculosis in the European Theater. Repeated spot roentgen-ray surveys of selected units by the Senior Consultant in Tuberculosis disclosed no rising incidence of this disease except to a limited degree among nurses over a year in the Theater. The release of RAMPs from Buchenwald and Dachau, among other festering detention camps, suddenly threw an enormous load of far advanced tuberculosis on our mobile and fixed hospitals. Its management in the interest of Allied military and dislocated civilian personnel is a tribute to American Medicine. The Senior Consultant in Tuberculosis organized the work in a most effective manner. The problems in nutrition imposed by the calculated starvation of prisoners by the Nazi were anticipated and met by the combined efforts of the Nutrition Section of the Preventive Medicine Division and experts in the clinical field from the Professional Services Division.

When the Medical Service assumed responsibility for the care of venereal diseases, the Surgeon General left a wise provision. These patients would be treated by the medical officer best qualified to meet their needs. While the

Medical Service could and did care for a majority of the luetic subjects, in many units the urologist continued to treat gonorrhea under the administrative supervision of the Chief of the Medical Service. The experience with the shifting therapy of these conditions differed in no wise from other theaters; but under the Senior Consultant in Dermatology the therapy of syphilis and gonorrhea was consolidated and advanced immeasurably as penicillin became the preferred agent.

The Senior Consultant in Neuropsychiatry marshalled the experience in other armies and in other theaters for the treatment of neuropsychiatric casualties in the European Theater of Operations. Special courses in elementary psychiatry were offered medical officers of tactical units. More advanced courses were given to divisional psychiatrists; but most effective were the lectures for line officers that gave them basic instruction in the recognition and prevention of combat exhaustion. In the field such educational agencies paid fine dividends in limiting losses from these causes.

Reviewing the medical experience of the European Theater of Operations certain salient features emerge. A plan of organization of professional service was evolved on the basis of earlier military experience. Time was afforded to perfect the steps of this organization. The geographic and topographic problems were minimized. The elements were not hostile. Hospitalization to the extent of 140,000 beds was laid on in the United Kingdom before D-Day. Transportation by air, road, rail and sea facilitated movement. The coördination of the several divisions of the Chief Surgeon's Office lent direction and impetus to the purely medical functions emanating from the Professional Services Division. No endemic disease nor serious epidemic was encountered. Superior measures of prevention further limited the incidence of disease. The sulfonamides and penicillin contributed immeasurably to the superb medical record of the Theater; but in the last analysis the largest single factor in the care of our sick was the quality of service that stemmed from the medical training of the past 25 years. Guard well the educational advantage won.

# SCRUB TYPHUS IN DUTCH NEW GUINEA \*

By EDWIN N. IRONS and HIRAM E. ARMSTRONG, *Chicago, Illinois*

IN the course of jungle operations in the islands of the Southwest Pacific, and in the China-Burma-India Theater, Allied forces encountered scrub typhus (Tsutsugamushi disease) in a variety of geographical conditions and with marked variations in the number and severity of cases and speed with which the outbreaks developed. This is a report on 1255 cases of scrub typhus contracted by U. S. Army personnel between June 18 and October 21, 1944 on Owi and Biak islands, off the coast of Dutch New Guinea. All cases were cared for in a 750 bed Army evacuation hospital located on Owi island. Particular interest in this group lies in the large number of cases and the relative mildness of the infection.

## ECOLOGY AND EPIDEMIOLOGY

The physical features of Owi and Biak islands favorable to the maintenance of the rat-mite-rat cycle of Tsutsugamushi disease have been described by Kohls et al.<sup>1</sup> In contrast to the circumscribed areas of open kunai grass which seemed to be the principal ecological condition associated with scrub typhus in British New Guinea and some neighboring islands, on Owi and Biak islands, abandoned coconut groves, native gardens overgrown with grass and shrubbery, and margins of clearings adjacent to rain forests harbored rats with their parasitic mites. On Biak island, they also seemed to favor corraline ridges covered with low growing trees and native vegetation. Previous outbreaks of scrub typhus among the Allied Forces in the Southwest Pacific Theater had not indicated such areas as actual or potential sources of infection. Because the earlier outbreaks came from infected foci of kunai grass, in later operations this type of area was carefully avoided or cleared and burned over when it became necessary to bivouac or station troops there. However, the epidemic to be described came under new conditions and developed to an extent that was of considerable military importance.

Operations against the enemy commenced early in June; the first cases of scrub typhus appeared in the week June 18 to 24. As personnel poured into the newly occupied areas, the case incidence rose to a peak of 184 cases in the week July 30 to August 5. The first scrub typhus infections in soldiers appeared at about the same time on Biak and Owi islands, but the incidence was less on Biak than on Owi, and the peak of infection on the former was reached about two weeks earlier. Although the area occupied on Owi island was much smaller than that on Biak, a large majority of the cases (891)

\* Received for publication September 26, 1946.



appeared on this heavily populated piece of land. A large proportion of the Fifth Air Force personnel (average strength 15,000), was located on Owi island. Seven hundred and sixteen cases of scrub typhus occurred in this group, indicating in a general way the incidence of infection.<sup>2</sup> A larger body of troops on Biak island consisting chiefly of infantry and service units, suffered a lower rate of infection. Many individual units suffered a much

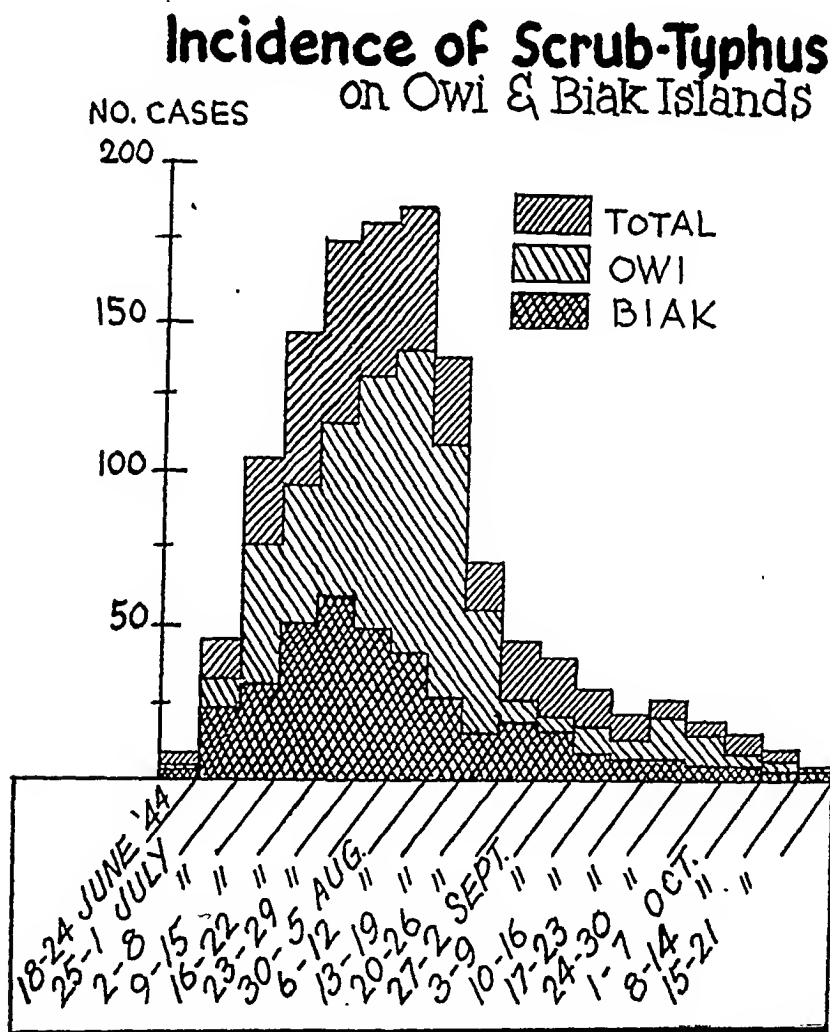


CHART 1. Incidence of scrub typhus on Owi and Biak islands. The case incidence is plotted by weeks and the total number of cases is subdivided into those from Owi and Biak islands.

higher incidence than the general average rate of infection, and in these units the maximum number of cases usually came about three weeks after the first cases were recognized. Within these groups, personnel in positions of leadership were ill in numbers sufficient to decrease these organizations' overall efficiency.

By the end of August, the rapid influx of troops to these new areas was over. The environmental conditions favorable for the maintenance of nat-

ural scrub typhus infection in rats and mites had been recognized and control measures of clearing brush and undergrowth from living areas had been undertaken. Individual protection by impregnation of uniforms with an emulsion of a mite repellent, dimethylphthallate, had also been instituted. These control measures, coupled with a more stabilized situation, diminished the rate of infection to sporadic cases during the middle of October. Chart 1 graphically shows the rapid increase of cases as troops entered infected areas on Owi and Biak islands, and the more gradual decline as environmental and individual control measures were carried out.

### ETIOLOGY

*Rickettsia orientalis* (Nagayo et al.), the causative agent of scrub typhus, is transmitted to man by the bite of an infected larval mite, in this case probably *Trombicula Fletcheri*, (Womersley and Heaslip,<sup>1</sup> 1943). The infection is hereditary in mites and is passed to successive generations of the animal reservoir, rats, one of the animals on which the larval form normally feeds. Man serves only as a casual host.

Rickettsiae may be readily isolated from the blood of patients in the febrile stage by intraperitoneal inoculation in white mice. Giemsa-stained smears of the peritoneal exudate of mice so infected show numerous intracellular rickettsiae. This material is infectious for other laboratory animals and the infection may be passed serially in mice by intraperitoneal or other routes of infection.

In this series, eight representative patients infected with scrub typhus were chosen for rickettsial study. All were prostrated with a moderately severe febrile illness varying in duration from two to 16 days at the time blood was withdrawn for mouse inoculation. An eschar was present in four and absent in the others. All showed varying degrees of generalized lymphadenopathy. Five manifested a typical mild erythematous rash during the febrile stage. Six of the eight complained of generalized aches, particularly in the back. One-half of the group had moderate cough, but none developed physical signs of pneumonitis or bronchopneumonia. One showed severe conjunctivitis. There were no severe mental changes, deafness or peripheral neuritis, nor was there jaundice. One patient's course was prolonged by malaria. The total duration of fever varied between nine and 21 days.

All eight groups of mice inoculated intraperitoneally with patients' blood, became infected with *Rickettsia orientalis*, but only four strains were of sufficient virulence to kill the mice so infected. This was in contrast to strains isolated elsewhere whose virulence was almost universally lethal for white mice. The groups of mice surviving were proved to be infected by further surviving challenge doses of 1000 MLD of virulent rickettsiae.<sup>3</sup> There seemed to be little difference clinically between the group of four

patients from whom strains were isolated and passed serially and the other group of four whose bloods produced an inapparent infection in white mice. Two in each group showed eschars, two did not. The days of illness when the bloods were inoculated into mice were roughly parallel in each group, as were the total durations of fever in each. However, all of the group whose bloods produced active transferable infection in mice had sufficient pulmonary involvement to show a cough, while the others did not. This clinical feature might distinguish the severity of infection in the two groups.

The four strains isolated were passed serially by intraperitoneal inoculation in white mice during a five month period. During this time the mice died on an average in 9 to 10 days. Strains of rickettsiae isolated in Papua, New Guinea and from Bat island and observed by us for periods of 15 and seven months were more virulent, killing infected mice on the average in seven and six days respectively. When compared to the Owi-Biak islands strain, this greater virulence was also demonstrated by a 100 to nearly 1000 fold increase in the MLD<sub>50</sub> titer for white mice. A similar difference in virulence was observed following intraperitoneal inoculation of infectious material in guinea pigs. The Bat island strain caused the highest mortality; the Owi-Biak island strain caused the lowest.

Recently Topping<sup>4</sup> showed cross immunity between strains of rickettsiae, isolated in Papua, New Guinea, Malaya, and from the Assam-Burma border, by inoculating guinea pigs, recovered from a scrub typhus infection, with one of the heterologous strains. Topping found one of the Papuan strains (case 9) least virulent and the Malayan strain the most virulent. He indicated that although cross immunity existed, this did not mean that strains were immunologically identical. Bengtson<sup>5</sup> illustrated this further by showing that serums of man and guinea pigs, recovered from scrub typhus infections, yielded much higher complement fixation titers with the homologous antigens than with antigens made from heterologous strains. She clearly differentiated serologically the Papuan (Karp) strain from the Assam-Burma (Gilliam) strain and indicated that the former was more virulent for white mice. Bell et al.<sup>6</sup> studied the antigenic relationship of three scrub typhus strains by cross neutralization tests. Antiserums produced in rabbits to two strains (Kostival from Papua and Seerangayee from Malaya) neutralized the homologous strain only, but antiserum produced in guinea pigs to Host 21 strains (isolated from mites collected in Papua) partially neutralized heterologous strains.

One of us demonstrated cross immunity between the Owi-Biak strain and a Papuan (Shope) strain by intraocular infections in rabbits.<sup>1</sup> In light of the work of others, this may be interpreted as a general cross immunity between strains of varying virulence, but more detailed study might show serological heterogeneity even in the presence of a common antigenic factor.

## PATHOLOGY

In this series of 1255 cases there were eight deaths, or a mortality rate of 0.6 per cent. All of these eight patients presented a typical severe scrub typhus course. Six of the group had a well defined eschar and all showed generalized lymphadenopathy. An erythematous rash was observed in seven of the eight patients. All complained of severe headache, and a cough occurred in six of the eight. Of this group with cough, all developed signs of pneumonitis or bronchopneumonia consisting of increased respiratory rates, varying degrees of cyanosis, dullness on percussion of the lung fields, particularly at the lung bases and medium to coarse râles over areas of diminished resonance. During the last days of illness, progressive rise in temperature to 106 to 108° F. occurred with increased pulse and respiratory rates, and fall in blood pressure. Death was probably due to a combination of myocardial and pulmonary insufficiency, and peripheral vascular collapse. The importance of peripheral vascular damage as a factor in fatal rickettsial disease has been emphasized recently by Woodward and Bland in their study of epidemic typhus.<sup>7</sup> Three of the patients manifested striking central nervous system changes characterized by clouded sensorium, delirium, episodes of motor activity and convulsions, signs of meningismus and coma. Here, fatal termination probably resulted in part from this marked central nervous system involvement. Two patients showed severe bleeding tendency, manifested by subcutaneous ecchymoses and hemorrhage in the gastrointestinal tract. Two other patients were jaundiced. The duration of illness before death, one patient excluded, ranged between 13 and 24 days. This excluded patient died on the thirty-second day of illness, with bacillary dysentery. The Weil-Felix reaction in this case rose from no titer on the tenth day of illness to 1:5120 on the twenty-sixth day. Histological examination revealed lesions consistent with a healing scrub typhus infection. For these reasons, this was considered a scrub typhus death, although the immediate cause was erosion and bleeding of the large intestine and toxemia (presumably due to bacillary dysentery). *Plasmodium vivax* malaria complicated the course of another patient.

Certain pathological changes, although not striking, characterized the postmortem picture in scrub typhus. The primary eschar, seen at the onset of illness, was present in varying stages of healing at death, but the rash had usually faded. There was frequently a yellow serous effusion, flecked with white exudate, ranging from 50 to 100 c.c. in the pericardial cavity, 200 to 800 c.c. in the pleural cavities and up to 1000 c.c. in the abdominal cavity. The mesenteric, tracheobronchial, retroperitoneal, inguinal, axillary and cervical lymph nodes were frequently enlarged and were grayish pink on cut section. In those patients with clinical signs of pneumonia or pneumonitis, the lungs showed the most marked change. They presented a dark purple mottled appearance, weighed between 500 and 1100 grams and dark

reddish-purple cut sections oozed copious amount of frothy blood fluid. When secondary bronchopneumonia supervened, there were areas of purulent consolidation. The heart showed little gross change, and presented the usual dull beefy red appearance on cut section. Occasionally there were subepicardial petechial hemorrhages. Scattered areas of punctate hemorrhage were also found in the gastrointestinal tract. The spleen was usually enlarged two to four times, and was soft and congested. In those patients showing central nervous signs and symptoms, the brains were slightly edematous with minute hemorrhages in the pons and brain stem, and the meningeal vessels were dilated. Kidneys and testes showed little or no gross change.

The histological picture in scrub typhus, as described by Settle et al.<sup>8</sup> was an acute, generalized endangiitis, vasculitis and perivasculitis which involved most of the organs of the body. Capillaries, arterioles and venules showed endothelial swelling or were thickened by proliferation. The perivascular infiltration was predominantly of plasma cells with some large mononuclear cells and lymphocytes; occasionally, there were polymorphonuclear leukocytes. The interstitial tissues showed varying degrees of edema, hemorrhage and cellular infiltration.

The most marked changes were in the heart which was involved with both a localized and diffuse myocarditis, most prominent in the interventricular septum. Vascular changes were pronounced, there were edema and cellular infiltration of the connective tissue and patchy myocardial degeneration, which varied from cloudy swelling to necrosis of muscle bundles.

The lungs showed interstitial edema and cellular infiltration, with hemorrhage. The alveoli contained edema fluid, occasional leukocytes and red blood cells. In areas of secondary bronchopneumonia, the alveoli and smaller bronchioles showed the characteristic purulent reaction due to bacteria.

In the kidneys were scattered areas of interstitial mononuclear cell infiltration, most frequently seen at the cortico-medullary junction. Some of the glomerular capillaries showed thickening and proliferation; occasionally there was glomerular ischemia, and crescent formation in the glomerular spaces. Areas of tubular epithelium showed cloudy swelling. In the medullary portion of the kidney were small areas of hemorrhage.

The most marked histological brain changes occurred in those patients with neurological signs and symptoms. The meningeal vessels showed a moderate perivascular round cell infiltration, and the small vessels of the brain substance showed a similar reaction in the perivascular sheaths. Infrequently small nodules, described as typical of typhus, occurred in the pons and brain stem and consisted of aggregations of irregularly placed mononuclear cells, glial cells and occasionally polymorphonuclear leukocytes. These nodules were related to small vessels and were associated with edema of the brain substance.

The primary eschar presented coagulation necrosis of the epidermis and superficial corium, and vasculitis and perivasculitis with infiltration of round cells and polymorphonuclear leukocytes. At times there was regeneration of epithelium, although the vascular changes beneath remained.

The spleen and lymph nodes showed an acute splenitis and adenitis, with congestion, edema, hemorrhage and infarction or focal necrosis. Other organs in the body exhibited lesser degrees of vascular change, mononuclear cell infiltration, and occasionally focal hemorrhage.

### VARIATIONS IN SCRUB TYPHUS

Case reports on scrub typhus occurring in New Guinea, India, China, Burma and Malaya<sup>9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19</sup> illustrate some of the clinical variations of this disease, and are summarized here. The groups selected were recently reported cases and dealt largely with military personnel. Thus factors influencing the severity of the disease such as youth or old age, sex, race, and intercurrent disease were somewhat reduced and the physical status of the personnel involved was fairly constant. While Lewthwaite's series dealt chiefly with Tamil laborers, of 250 only 20 patients were over 40 years of age. The series reported by Boyd, Machella et al., Tattersall, and Agress et al., included many Orientals. Diseases affecting the course of illness such as malaria, dysentery and parasitic infection were more common among these Asiatic peoples than among the whites.

Reports of earlier case series from regions discussed here and others from Sumatra, Japan, Formosa and its neighboring islands concerned general populations, i.e. male and female, children, vigorous adults, and older people, healthy and debilitated individuals. Among these, the mortality rate was frequently higher and reached 25 to 40 per cent in some instances.

The mortality rates of the groups summarized here, as shown in chart 2, ranged from less than 1 per cent in New Guinea and India to 15 per cent in Malaya. Within some groups there was a considerable variation in mortality. Sangster reported a rate of 3.2 per cent in his first 125 patients from New Guinea, whereas in the next 95 patients, whose disease was contracted farther west in the Ramu Valley, he reported a rate of 14.7 per cent. Similarly, in New Guinea, Williams found a death rate of 1.5 per cent in the first 200 patients with an increase to 25 per cent in the next 150 patients. He attributed this higher rate in part to physical exhaustion of the troops and to a high incidence of malaria and dysentery. Agress, in Assam and North Burma, observed a mortality of 4 per cent in the first group of patients studied with an increase to 18 per cent in the second group. In five groups of patients studied in Assam and Burma by Sayen et al.<sup>20</sup> the mortality varied from none to 16 per cent. Although these patients contracted their disease in various infected foci in Assam and Burma, the writers attributed the differences in mortality to the variation in physical status of the several groups concerned.

## Summary of Scrub

Writer	Irons and Armstrong	Boyd	Machella and Forrester	Berry et al.	Mendell	Browning et al.
Location	Owi-Biak Islands	India	China	New Guinea	New Guinea	New Guinea
Year	1944	1935	1943-44	1943-44		1944
No. cases	1255	35	64	195 [85 new cases]	75	173
Mortality	0.6%	Nil	1.6%	[New] 2.4%	2.7%	3.5%
Duration of fever	Ave. 13.7 days [681 cases] 52% 1-13 days 37% 14-20 days 11% 21-30 days	Average: 14.2 days	Average: Chinese 18.3 days American 16 days	Average: 16-17 days	10% 7-10 days 61% 10-20 days 24% 20-30 days	3% <14 days 80% 14-21 days 17% >21 days
Cough, bronchitis and pneumonitis	7.6%		40%		51%	
Broncho-pneumonia and pulmonary complications	1.3%			11.7%		17%
Mental and other central nervous system changes	4.1%	Common	12.5%		48%	
Deafness	0.8%	Nil		33.3%	35%	20%
Peripheral neuritis	0.2%					
Eschar	51%	Nil	67%	80%	68%	80%
Rash	35%	Europ. 71.1% Indians 7.1%	51.5%	Almost all	78%	35%
Adenitis	97%	Nil	93.7%	Usual	95%	
Headache	71%	All	76%			92%
Chill	6.8%		68%			47%
Weil-Felix reaction	Ave. positive 8-10 days [1003 tests]		Ave. positive 14 days	Most: Rising titer or 1:160+	Majority 1:180+	Most: Rising titer or 1:180+

CHART 2. Summary of scrub typhus case reports.  
data of the several writers and arranged in this

Clinical and rickettsial studies have revealed circumscribed areas which harbored particularly virulent forms of scrub typhus. Such areas have been found in Malaya, on Goodenough island,\* and Bat island,\*\* and near Buna and in parts of the Ramu Valley in New Guinea. On the other hand, areas not far removed from these foci of virulent infection harbored a much milder

\* On Goodenough island, during a 4.5 month period in October 1943 through January 1944, more than two-thirds of the cases of an epidemic of scrub typhus were contracted in a hospital area. The total cases numbered 69. The mortality, 27.5 per cent, indicated a virulent form of infection.<sup>1</sup>

\*\*South Bat island, in the Purdy group, located 60 miles south of the Admiralty island, was abandoned in April 1944 because of a high incidence of scrub typhus. Among 41 traceable individuals who visited or were stationed on Bat island, there were 26 cases of infection with two fatalities.<sup>21</sup>

Typhus Case Reports

Tattersall	Menon and Ibbotson	Sangster and Kay	Williams et al.	Lipman et al.	Agress and Evans	Lewthwaite and Savor
India and Burma	N.E. Burma	New Guinea	New Guinea	New Guinea	Assam and Burma	Malaya
1943-44	1944-45	1943-44	1942-44	1943-44	1943-44	1940
500 [200 Europeans]	110	235	626	200	86	250 [15 Europeans]
6% [1000 cases]	8.2%	Ave. 8.5% Oct.-Dec. '43 [125] 3.2% Jan.-Mar. '44 [95] 14.7% Apr.-May '44 [15] 13.2%	Ave. 9.7% 1st 100 cases 1% 2nd 100 cases 2% 3rd 150 cases 25% Last 276 cases 7.2%	10%	Ave. 10% 1st group 55 cases 4% 2nd group 31 cases 18%	15%
Average: 18 days	Average: 15.7 days 23% <10 days Range 5-29 days	Average: 14-21 days Mild 8-10 days	Usual 12-20 days [508 cases] 2% 4-8 days 54% 14-18 days 3% 26-40 days	Ave.: 14-18 days	Average: Gr'p 1-18 days Gr'p 2-21 days	Average: 12-15 days
68%	50%	Common		20%	40%	80%
	6.4%			9%		13%
100%	50%				Mild—almost constant	35%
		15%			28%	Slight 50% Mod. 8% Severe 8% } 66%
2%	5.5%	0.8%		5%		
11%	56%	41%	59%	80%	78%	5%
Europ. 64% Indians 31%	64%	52%	65%	85%	Chinese 31%	Europeans—all Indians—some
92%	98%	Almost universal	66%	98%	94%	40%
100%	100%				86%	92%
					83%	
55% pos. 11 days 80% pos. 15 days 99% pos. 19 days 500 cases 800 tests	Titer of 1:125 or over in 82%	Ave. positive 12-16 days Earliest positive 6 days Latest positive 26 days	Titer of 1:150 or over in 86%	Positive 9-36 days	Ave. positive 14 days 80% positive 62 patients	Titer of 1:125+ or rise in titer in 99%

This summary was prepared from the published chart on the basis of increasing mortality rates.

type. No focus of severe infection was encountered in Dutch New Guinea, although there was a mortality of 3.7 per cent in an epidemic of 931 cases of scrub typhus reported from Sansapor, Dutch New Guinea.<sup>22</sup>

In a comparative rickettsial study in guinea pigs, Topping found the Seerangayee strain from Malaya to be most virulent for these animals. The Gilliam strain, from the Assam-Burma border, was next in virulence for guinea pigs, while the Imphal strain from India was least virulent. The Karp and Case 9 strains from Papua were intermediate in virulence to the Gilliam and Imphal strains. In chick embryos, Bengtson<sup>5</sup> found the Assam-Burma (Gilliam) strain the most and the Indian (Imphal) strain the least virulent. Karp, Seerangayee and Case 9 strains were intermediate in reac-



tion. Rickettsial studies in white mice, performed by one of the authors, showed a Bat island strain to be most virulent and strains from Owi-Biak islands to be least virulent.<sup>8</sup> The Shope strain from Papua was somewhat less virulent than the Bat island strain.

On review of available reports, some of the clinical features of scrub typhus presented by various writers could be correlated with variation in mortality rates and differences in virulence of the causative rickettsial agent for laboratory animals. The average duration of fever ranged from 13.7 days in the less severely ill patients to 21 days in those more severely affected. Cough and the minimal signs of pneumonitis seen in scrub typhus occurred in all the series reported, but the incidence seemed rather variable. Also, secondary bronchopneumonia due to pyogenic organisms and other pulmonary complications occurred with varying frequency. This may be due in part to the manner in which the several authors compiled and presented their data. Although milder cases were separated from the more severe on the basis of locale and mortality, the signs and symptoms of the disease in the different groups were combined. However, detectable pulmonary change was less frequent in our series than in others. Similarly, nervous system involvement characterized by delirium and other mental change, meningismus, eighth nerve deafness and peripheral neuritis was less frequent in our group of patients than in other series in which these changes were discussed. It is significant that many authors commented on the marked severity of illness in those patients with outstanding cardio-respiratory or nervous system involvement.

The appearance of a primary eschar or erythematous rash typical of scrub typhus seemed to have little or no correlation with the severity of illness. One of the determining factors in the development and detection of rash and eschar seemed to be the color of the patient's skin. Rash and eschar were relatively frequent in the white race, whereas they were infrequently reported in the yellow or brown races. However, Anderson and Wing reported 70 per cent eschar and 43 per cent rash in a series of 49 cases of scrub typhus in Melanesians.<sup>23</sup> Regional and generalized lymphadenitis was almost universally present in most series.

The agglutination of *Proteus* OXK by patients' serums, the Weil-Felix reaction, was a diagnostic aid in most of the series. The reaction became positive on an average between the eighth and tenth days in our series, whereas in others of greater severity and higher mortality, the average positive developed five or more days later.

#### CLINICAL DATA

The 1255 cases studied in this series were all Army personnel. The great majority were young adults previously in good physical condition. Following the onset of illness, they were hospitalized with reasonable promptness and lengthy evacuation was not necessary as they were all cared for in

the immediate area. Malaria and dysentery were seen in a small proportion of those afflicted with scrub typhus, but these intercurrent infections were of relatively minor importance in the final outcome of the disease in the group as a whole.

The incubation period of scrub typhus in this outbreak appeared to be usually between 9 and 21 days. In many mild cases it was apparently longer but this may well have been due to the fact that the onset of illness was insidious, making it difficult for the patient exactly to date his first symptoms. Indeed, many continued their duties for days after the first mild effects of the disease were felt and some were not hospitalized until an asthenic state, usually seen early in convalescence, developed.

The onset of scrub typhus in the majority of patients was marked by generalized headache (71 per cent) and fever. Mild to moderate prostration was common, and 36 per cent of patients experienced general malaise frequently associated with severe backache. Also, at onset, patients often complained of chilliness, and frank shaking chills occurred in 6.8 per cent.

Fever varied markedly in height and duration. Many of the less severely ill had irregular low grade fever for only a few days. Many other mild cases showed a sustained moderate elevation in temperature for a somewhat longer period. In the more protracted febrile cases, the fever curve rose in a step-like fashion to a maximum varying between 102° and 106° F. The course of pyrexia in these cases closely resembled the typhoid-like fever curves seen in many of the severely ill patients, who contracted the disease in Papua and the Australian Mandated Territory in New Guinea. Temperature returned to normal by lysis of a few days' duration. In a group of 483 patients on whom temperature readings were taken at regular intervals daily, the highest fevers were observed most frequently between the seventh and eleventh days, with the ninth day as an average. The extremes in height of fever ranged between the first and twentieth days. That is, the highest recorded temperature in some patients was seen as early as the first day of illness, whereas in others the maximum temperature occurred as late as the twentieth day. There was also a great range in the total duration of the fever, from one to 30 days. However, the usual duration of pyrexia was eight to 18 days, with an average of 13.7 days. A secondary temperature rise, also noted by some other writers, occurred in 2.2 per cent of the total cases. This rise started two to 10 days after the subsidence of the initial fever, when the patient appeared convalescent, and lasted a few days. It usually occurred in those patients whose original illness was relatively slight, and was accompanied by mild symptoms.

Charts 3 and 4 present graphically the incidence of highest fever in 483 cases and the total duration of fever in 681 cases.

The pulse rate was only moderately elevated during the first week of illness, but during the second and subsequent weeks, particularly in more severely ill patients, pulse rates of 100 to 120 per minute were not infrequent.

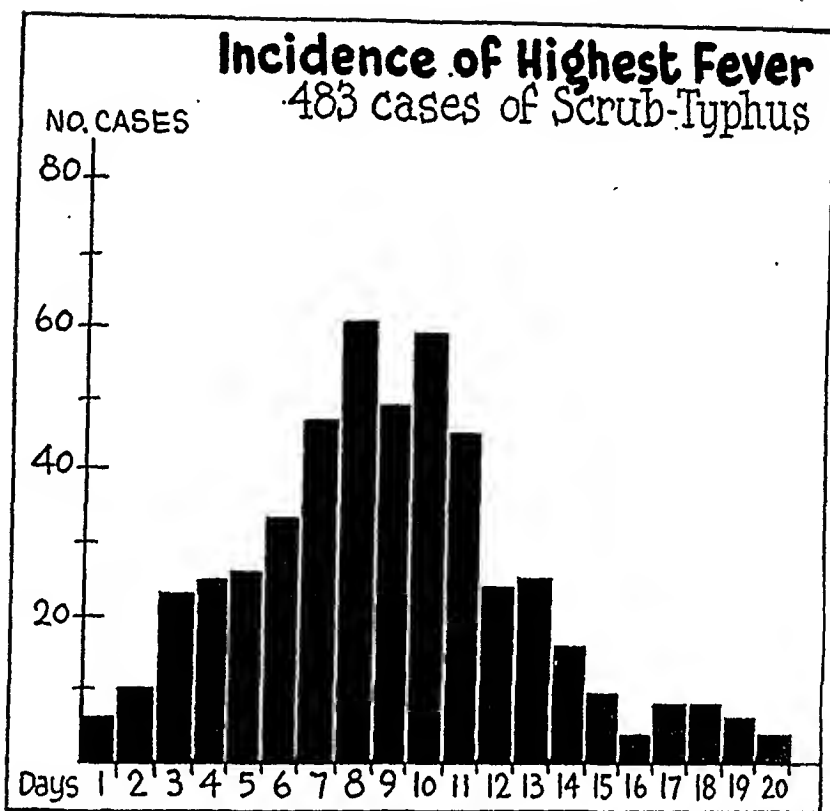


CHART 3. Incidence of highest fever in 483 cases of scrub typhus based on temperature readings taken at four hour intervals.

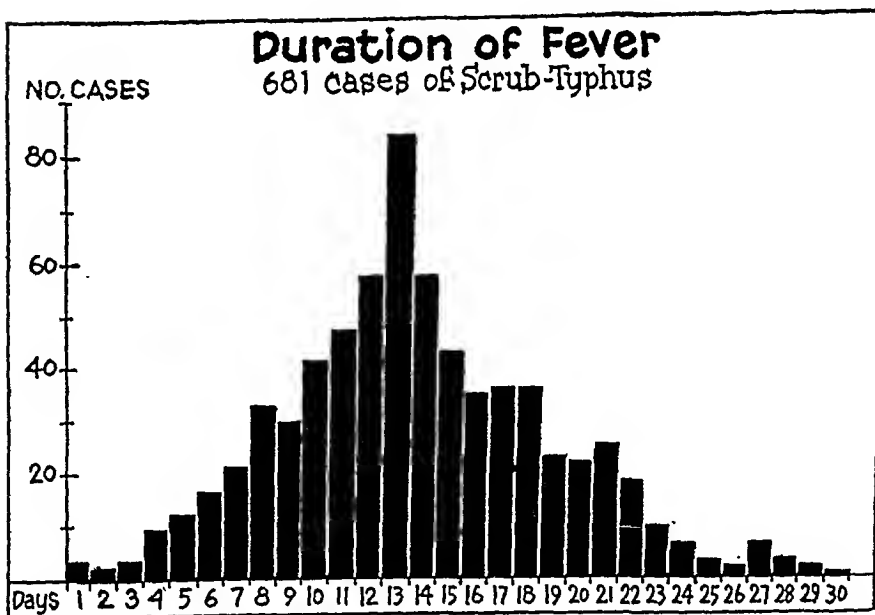


CHART 4. Duration of fever in 681 cases of scrub typhus. Note the maximum incidence on the thirteenth day.

Tachycardia usually subsided with defervescence, but during the early weeks of convalescence it was not uncommon for patients to complain of palpitation associated with a rapid pulse.

A primary eschar, the initial point of rickettsial invasion at the site of attachment of an infected mite, was seen in 51 per cent of patients. Lewthwaite and Savor first showed immunological identity between rickettsial infections with and without eschar,<sup>18</sup> and repeated clinical and laboratory observations have since confirmed the existence of scrub typhus in the absence of a primary lesion. When present, the eschar was a distinct diagnostic aid. Typically, it measured about a centimeter in diameter, with a raised erythematous border and a black necrotic center. This necrotic area was absent in eschars found in the warm, moist skin folds of the axilla, perineum and other similar locations. In these sites the eschar appeared as a shallow depressed ulcer with well demarcated erythematous border and purulent base. In 23 cases, two or more ulcers were observed simultaneously. As the disease regressed, the necrotic material in the eschar sloughed and epithelium gradually filled the defect. This process was slow and in many cases persisted to early convalescence.

Although mites did not usually crawl from the ground up natural objects such as grass or brush, they were noted to crawl rapidly on foreign objects placed in their natural habitat. An observer on an army cot was reached 1.5 to five minutes after the cot was placed in proximity to mites. On cloth used to make fatigue suits, a group of six mites traveled an average of 11 inches in five minutes.<sup>1</sup> When these mites attacked man, they seemed to have a predilection for the region of pressure between clothing and skin such as the belt line, ankles and beneath leggings. Thus it appeared that the site of the mite attachment was dependent on at least two factors: the availability of a foreign object on which the mites crawled seeking a suitable place, and, secondly, an area of pressure in which they attached.

The distribution of 651 eschars seemed to reflect the natural habits of the mites. Forty-five per cent of all eschars were found on the feet and legs. When soldiers walked or stood in a mite infested area, the legs provided the most accessible location on the body to mites and there were ample pressure areas beneath shoes, leggings and trousers. The folds of skin in the genital, inguinal, axillary, antecubital and popliteal regions formed natural pressure points, and mites seemed to have an affinity for these warm moist areas. Thirty-eight per cent of eschars occurred here although this percentage of mite attachment was much greater than the percentage of body surface represented in these areas. Another general pressure area was at the belt line and seat of trousers. Corresponding to this, 8 per cent of eschars were located on the lower abdomen, iliac crests, lower back and buttocks. The remainder, 9 per cent of eschars, were distributed over the rest of the body. Chart 5 gives a more detailed picture of eschar distribution. Figure 1 shows a typical eschar with black necrotic center located on the buttocks. Figure

2 represents an eschar with a purulent base but without a necrotic center, situated in the antecubital fossa.

Accompanying the primary eschars were varying degrees of adenopathy of those lymph glands which drained the sites of infection. Not infrequently there was associated tenderness, but only rarely was there suppurative change due to secondary pyogenic invasion of these regional glands. Lymph gland enlargement was found in 97 per cent of patients.

Another typical sign was the erythematous rash frequently found in scrub typhus. Between the fourth and eighth days of illness, the dusky

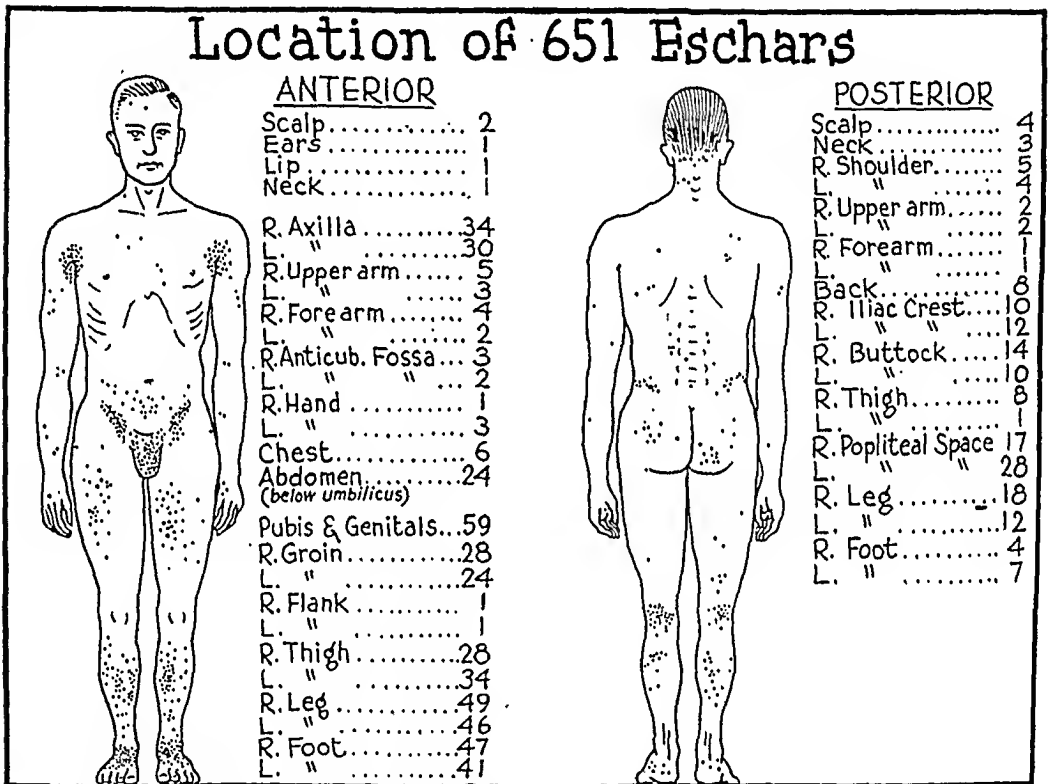


CHART 5. Location of 651 eschars. Note the concentration of eschars in regions of skin folds and pressure points. All eschars found in the axillary, genital and perineal regions are shown on the anterior figure.

red macules appeared characteristically on the trunk and to a lesser degree on the arms and legs. The average time of onset of the rash was 5.6 days after the first symptoms developed. In seven cases, the rash appeared with the onset of the disease, while in 11 cases the rash occurred on the tenth day of illness or later. The maximum time between onset of symptoms and the appearance of a rash was 14 days. The rash usually lasted two to three days, but not infrequently it appeared and faded within 24 hours. Occasionally a slight brown pigmentation remained for a short while after the erythema faded, but a hemorrhagic tendency was not noted immediately con-

nected with the rash. Of the 1255 cases in the group, a rash was found in 439 or 35 per cent.

Cough occurred infrequently in this series, 7.6 per cent of cases, in comparison to its common occurrence in scrub typhus patients seen elsewhere. Pnéumonitis, manifested by medium and fine moist râles over the lower lobes, was demonstrated in only a few of the sickest patients. As a reflection of the lowered incidence of marked pulmonary involvement, secondary bronchopneumonia due to pyogenic organisms was seen in only 1.3 per cent of cases.

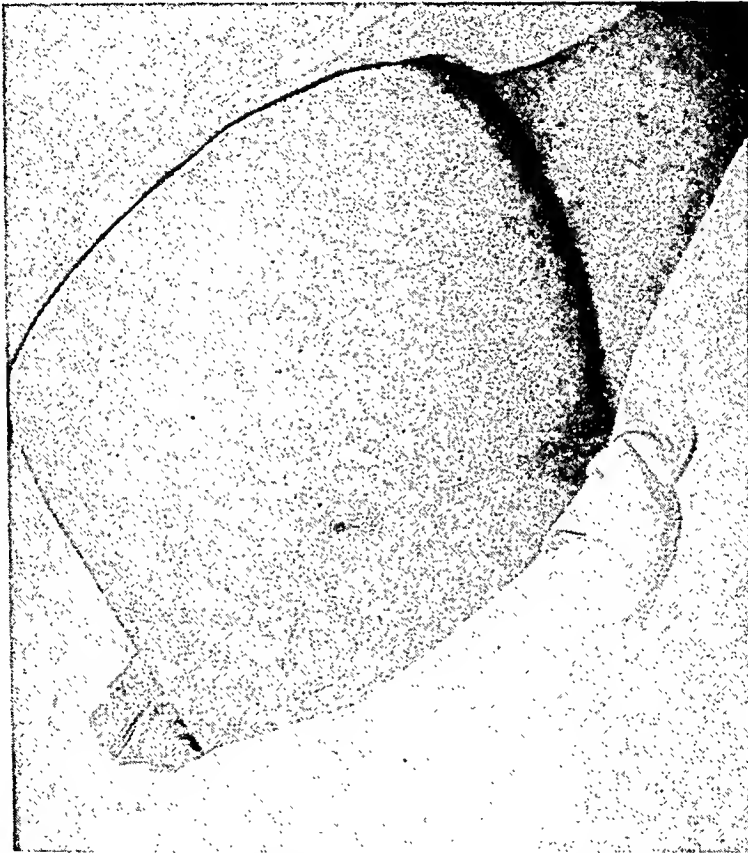


FIG. 1. Eschar on left buttock. Note the black, necrotic center surrounded by a zone of erythema (sixth day of illness).

Similarly, there was a low incidence of severe nervous system involvement. Delirium, confusion, convulsions, and meningismus together occurred in only 4.1 per cent of all cases, although 71 per cent of patients complained of headache. Deafness and peripheral neuritis, not infrequent in the usual cases of severe scrub typhus, appeared in only 0.8 and 0.2 per cent respectively.

The gastrointestinal tract and kidneys were affected clinically in only a small proportion of cases, 6.5 and 1.2 per cent respectively. Nausea and vomiting, and diarrhea followed by constipation, were the usual gastro-

intestinal disturbances. Very rarely was there sufficient bleeding to produce tarry stools. Slight to moderate hematuria, and albuminuria sometimes associated with ankle edema, were the chief signs of kidney involvement. All cleared early in convalescence.

Weil-Felix tests, using a 0.1 per cent formalized culture of *Proteus* OXK suspended in physiological salt solution, were performed on the serums of patients in all stages of the disease, ranging from the first to the eightieth

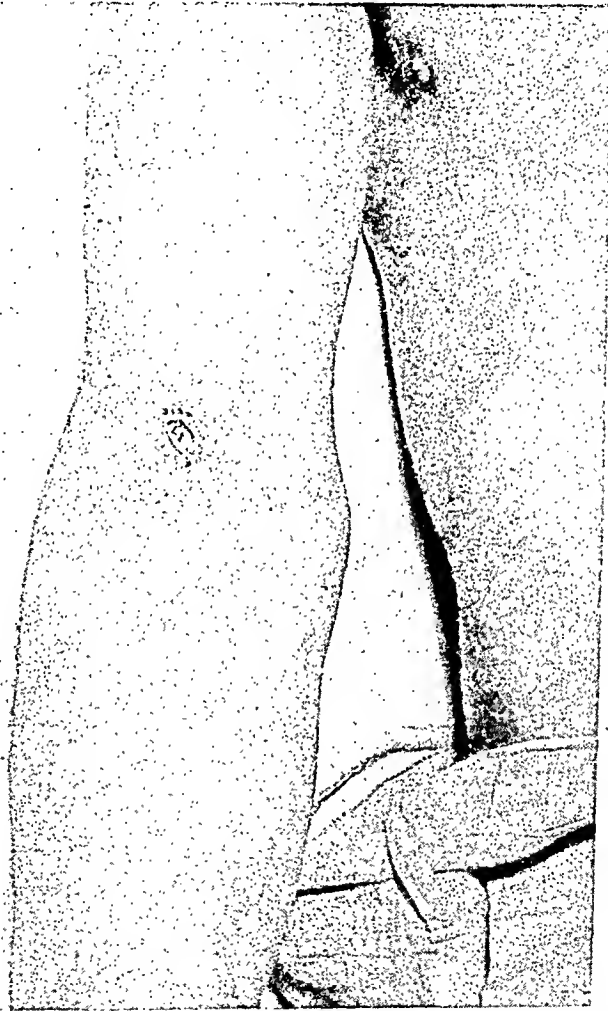


FIG. 2. Eschar in right antecubital fossa. Note purulent base and lack of black center (twelfth day of illness).

day of illness. During the first week, 30 per cent of tests were positive, in the second 63 per cent, while in the third the positive tests rose to 87.2 per cent and fell slightly to 82.8 per cent positive in the fourth week. The titers observed ranged from zero to 1:10240. During the first week the lower titers predominated whereas the proportion of high titers was greater in the second and third weeks. Thereafter, the incidence of positive tests and the height of titer in these tests gradually declined, but positive reactions were

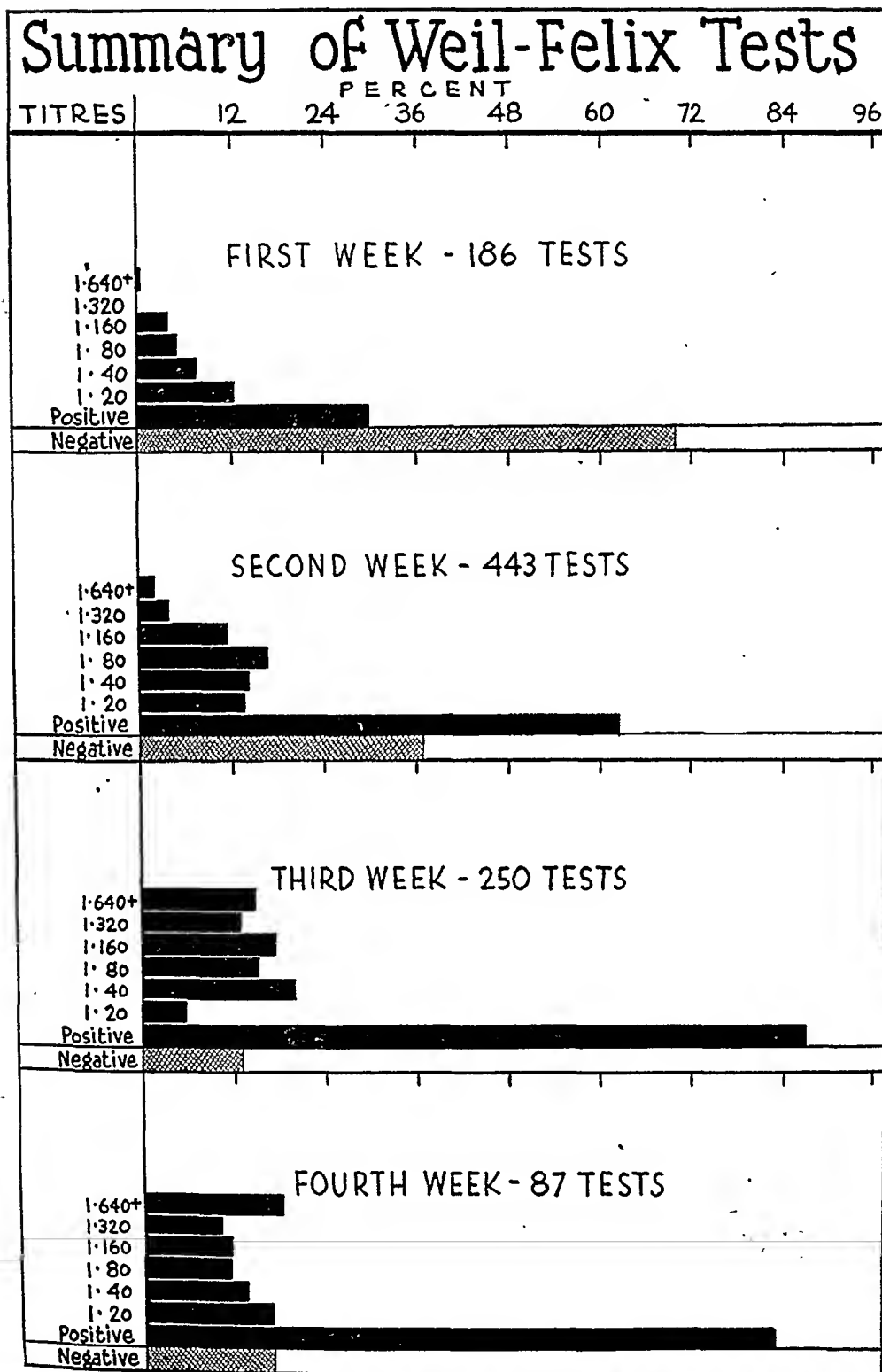


CHART 6. Summary of Weil-Felix tests. The progressive rise in titer is particularly prominent in the second and third weeks.



found two and one-half months after onset of illness. The average initial positive Weil-Felix reaction occurred between the eighth and tenth days of the disease, and reflected again the relative mildness of this particular epidemic. Chart 6 summarizes Weil-Felix tests performed in the first four weeks of illness. A rising OXK titer was observed in over 200 cases, but the remainder of tests represented single observations.

Leukocyte counts ranged between 2,600 and 15,000. Many counts showed a leukopenia with a relative or absolute lymphocytosis. Those patients with secondary bronchopneumonia, or other pyogenic infections, developed a polymorphonuclear leukocytosis. Fall in either hemoglobin or erythrocytes was infrequent.

The urine was usually normal, although sometimes traces of albumin were observed. One case of frank hematuria occurred and small to moderate amounts of albumin were found in the urines of some cases with peripheral edema.

Thirty-nine, or 3.1 per cent of cases showed slight to moderate elevation of the icteric index, which ranged from 10 to 40. Although moderate elevation of the icteric index is occasionally seen in scrub typhus, we thought a concomitant infectious hepatitis complicated the course of at least some patients, as during the same period over 1,000 soldiers from the same commands were under treatment in the hospital for this disease.

Treatment of this group of scrub typhus patients was largely symptomatic. During the febrile period, complete bed rest was the rule. Fluids were forced and supplemented if necessary by intravenous normal saline solution. Extra salt was administered by mouth in many cases. The most appetizing and nourishing diet possible under the circumstances was provided, but the majority of patients lost weight. Sedatives and analgesics were used sparingly. Early in convalescence the mildest cases were returned to their units and the others were evacuated to more fixed hospital installations.

Although we were unable to follow most of the patients during convalescence, a few were readmitted to the hospital two to three months after the initial infection because of asthenia. These patients complained chiefly of weakness, palpitation and easy fatigability. There was little to be observed except weight loss and in some instances a rapid pulse rate. Under a regimen of graded exercise most of these patients improved. None developed signs of cardiac failure. Although not within the realm of this report, it is significant to note that clinicians who studied convalescent scrub typhus patients failed to detect permanent myocardial damage or other persistent late sequelae.<sup>24, 25, 26, 27, 28</sup>

## SUMMARY

1. Outbreaks of scrub typhus have been observed under a variety of ecological conditions, sometimes under previously unrecognized circum-

stances; and the disease in different outbreaks has exhibited varying degrees of severity.

2. The degree and extent of natural infections in mites and rodents and the virulence of the infectious agent *Rickettsia orientalis*, in different localities has shown similar variations.

3. Clinical, laboratory and pathological studies are presented, on a group of 1255 patients with typical scrub typhus infection of a relatively mild type.

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# THE TREATMENT OF ACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN \*

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PRIOR to the use of penicillin, the establishment of a diagnosis of acute bacterial endocarditis was tantamount to prophesying the patient's death within one to six weeks. In the literature we have found reference to 40 patients with acute bacterial endocarditis who have been treated with penicillin (table 1).<sup>1-12</sup> Among the 25 patients whose infection was caused by a *Staphylococcus aureus* all but five died. Four of the patients with pneumococcal endocarditis died and two recovered. Five of the seven patients with hemolytic streptococcal endocarditis died, whereas death was reported in the case of one patient with gonococcal endocarditis. Recently a report of a case of meningococcal endocarditis which terminated fatally was published.

We have treated eight patients with acute bacterial endocarditis with penicillin (table 2). Five patients died, the diagnosis being confirmed by necropsy. In the three patients who recovered, the clinical course satisfied the criteria established for the diagnosis of this disease. Since our results appear encouraging we are reporting our experiences in the treatment of these eight patients.

## METHOD OF STUDY

Specimens of blood for culture were taken repeatedly from each patient. In every instance two or three positive blood cultures had been obtained before penicillin was started. In two patients, one of whom had been accustomed to taking heroin intravenously, the causative organism was a *Staphylococcus aureus*. A *Staphylococcus albus* was isolated from the blood of five patients. The source of the infection in one of these patients was undoubtedly a chronic pyelonephritis, three were heroin addicts, and in the fifth the source of the infection could not be determined. In the case of the eighth patient, who had pneumonia and meningitis, a type 12 pneumococcus was isolated from the sputum, cerebrospinal fluid and the blood stream.

The sensitivity of two strains of *Staphylococcus albus* was determined before treatment was begun. In each case the initial dosage was the amount estimated as necessary to maintain a constant bactericidal level for each organism, as judged by its sensitivity. These doses were apparently inadequate since the infection persisted and the resistance of each organism to penicillin was found to have increased. The resistance of the hemolytic,

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coagulase-positive *Staphylococcus albus*, obtained from the patient E. R., which had an original sensitivity of 0.39 unit per cubic centimeter increased 16-fold, whereas the resistance of the hemolytic, coagulase-negative *Staphylococcus albus*, obtained from the patient L. M., increased eight-fold, during the time these patients were being treated. The sensitivity of the organisms isolated from the remaining six patients was not determined, and the initial dosage-schedule was established empirically on the basis of past experience with the use of penicillin in the treatment of infections due to similar organisms. The initial dose for all eight patients varied between 5,000 and 30,000 units every two to three hours intramuscularly or 200,000 units per day by continuous intramuscular injection. It was necessary to increase the dose in several of the patients in order to control the infection. The largest dose given was 2,000,000 units daily by continuous intramuscular infusion.

TABLE I

Summary of Reported Cases of Acute Endocarditis Treated with Penicillin

Investigator	Number of Cases	Causative Organism	Duration of Therapy (Days)	Total Doses (Units)	Results	
					Recover- ed	Died
Case Record No. 29162 Mass. Gen. Hosp. <sup>1</sup>	1	<i>Staphylococcus aureus</i>	not given	large doses	0	1
Case Record No. 29371 Mass. Gen. Hosp. <sup>2</sup>	1	<i>Staphylococcus aureus</i>	10 hours	200,000	0	1
Keefer et al. <sup>3</sup>	9	<i>Staphylococcus aureus</i>	4 to 52	270,000 to 2,340,000	0	9
Herrell <sup>4</sup>	2	<i>Staphylococcus aureus</i>	not given	not given	0	2
Dawson and Hobby <sup>5</sup>	1	<i>Staphylococcus aureus</i>	3	480,000	0	1
Harford et al. <sup>6</sup>	2	<i>Staphylococcus aureus</i>	6 to 13	270,000 to 3,157,000	0	2
Meads et al. <sup>7</sup>	1	<i>Staphylococcus aureus</i>	16	3,820,000	0	1
Dolphin and Cruickshank <sup>8</sup>	3	<i>Staphylococcus aureus</i>	12 to 24	646,000 to 2,044,000	2	1
Anderson <sup>9</sup>	1	<i>Staphylococcus aureus</i>	5	1,000,000	0	1
Glaser et al. <sup>10</sup>	4	<i>Staphylococcus aureus</i>	6 to 35	270,000 to 2,340,000	3	1

TABLE I—Continued

Investigator	Number of Cases	Causative Organism	Duration of Therapy (Days)	Total Doses (Units)	Results	
					Recovered	Died
Present series	2	<i>Staphylococcus aureus</i>	1/8 to 56	25,000 to 13,440,000	1	1
Present series	5	<i>Staphylococcus albus</i>	1 to 107	865,000 to 81,120,000	2	3
Meads et al. <sup>7</sup>	2	Hemolytic streptococcus	1/4 to 14	30,000 to 445,000	1	1
Dolphin and Cruickshank <sup>8</sup>	3	Hemolytic streptococcus	10 to 15	960,000 to 2,300,000	3*	0
Anderson <sup>9</sup>	1	Hemolytic streptococcus	8	960,000	0	1
Cataldo <sup>11</sup>	1	Hemolytic streptococcus	11	1,420,000	1	0
Dawson and Hobby <sup>5</sup>	3	Pneumococcus	3 to 7½	172,500 to 384,000	0	3
Meads et al. <sup>7</sup>	3	Pneumococcus	6 to 18	975,000 to 3,285,000	2	1
Present series	1	Pneumococcus	27	1,040,000	0	1
Meads et al. <sup>7</sup>	1	Gonococcus	3	330,000	0	1
Firestone <sup>12</sup>	1	Meningococcus	not given	not given	0	1

\* One patient died later with evidence of healed endocarditis.

Since others,<sup>13</sup> as well as two of us,<sup>14</sup> have not encountered relapses in patients with subacute bacterial endocarditis treated with penicillin for eight consecutive weeks, it was decided to treat all patients with acute endocarditis for this same length of time.

## RESULTS

Patients who are adequately treated with penicillin may die of overwhelming infection, congestive heart failure or embolic phenomena. Three of our patients, E. R., W. W. and J. M., all of whom were treated for two days or less, died as a result of the infection itself. A fourth patient, O. B., received inadequate dosages. At the time this patient was under treatment the supply of penicillin was scarce and she received 5,000 to 10,000 units every two to three hours intramuscularly. One patient, F. B., with aortic

TABLE II  
Results of Penicillin Therapy in Eight Patients with Acute Endocarditis

Patient	Age	Sex	Color	Source of Infection	Duration of Infection (Days)	Causative Organism	Hemolysis	Coagulate	Valves Involved	Other Diseases	Complications Which Developed During Treatment	Duration of Treatment (Days)	Results	Follow-up
W. W.	13	M	W	Unknown	8	<i>Staphylococcus aureus</i>	Positive		Mitral	Rheumatic heart disease	Embolism of left popliteal and dorsalis pedis arteries	1/8	Died	Autopsy
J. F.	35	M	N	Heroin Addict	7	<i>Staphylococcus aureus</i>	Negative		Tricuspid	Toxic nephritis Skin abscesses	Pulmonary infarction	56	Recovered	20 months
E. R.	36	M	N	Unknown	8	<i>Staphylococcus albus</i>	Positive	Positive	Mitral Aortic	Rheumatic heart disease	Cerebral and splenic infarction	1	Died	Autopsy
J. M.	62	M	N	Pyelonephritis	56	<i>Staphylococcus albus</i>	Positive		Mitral	Arterio-sclerosis	Renal and splenic infarction	2	Died	Autopsy
O. B.	25	F	N	Heroin Addict	21	<i>Staphylococcus albus</i>	Negative	Positive	Tricuspid	Pregnancy Exfoliative dermatitis	Multiple septic infarctions	8	Died	Autopsy
A. S.	38	M	N	Heroin Addict	21	<i>Staphylococcus albus</i>	Negative		Tricuspid	Malaria	Pulmonary infarction	56	Recovered	20 months
L. M.	38	F	N	Heroin Addict	14	<i>Staphylococcus albus</i>	Positive	Negative	Tricuspid	Malaria	Pulmonary infarction	107	Recovered	7 months
F. B.	43	M	N	Pneumonia	40	Pneumococcus, Type 12			Aortic	Meningitis	Congestive heart failure	27	Died	Autopsy

valve involvement, died suddenly as the result of acute left ventricular failure following severe exertion at a time when the infection had apparently been brought under control by penicillin. The three patients who recovered were treated continuously for at least 56 days.

Although embolic episodes occurred in all but one of our patients, no deaths could be attributed directly to these complications. Four patients had clinical and roentgenological evidences of pulmonary infarction, and all of these had involvement of the tricuspid valve. Splenic infarcts were observed in three patients, renal infarcts in two and occlusion of the left popliteal and dorsalis pedis arteries in one.

Acute bacterial endocarditis may affect hearts previously undamaged but it occurs more frequently in those already affected with rheumatic or congenital lesions. There was evidence of a preëxisting heart lesion in two of our patients. In patient W.W. there was a history of rheumatic fever three years prior to admission, and at necropsy there was evidence of rheumatic mitral valvulitis. In patient E. R. there was no history of rheumatic fever but rheumatic disease of the mitral valve was present at autopsy.

An analysis of data concerning the valves affected revealed that one patient had involvement of the aortic valve, two of the mitral valve, and another of both of these valves. The valve most commonly involved in this group of patients was the tricuspid, this being the site of the infection in five patients.

Other diseases were present in seven of the eight patients. The one disease which offered the most difficulty in differential diagnosis initially, and as a possible cause of fever during therapy, was malaria. This infection has been found frequently in heroin addicts in this hospital, and as has been mentioned before, five of our patients were heroin addicts. Two of the patients developed fever and chills during treatment, and it was thought that the endocarditis had relapsed. However, repeated blood cultures on media containing penicillinase showed no growth, and eventually malaria parasites were found in blood smears. Both patients recovered after atabrine therapy.

Summaries of the histories of the three patients who have recovered are presented.

#### CASE REPORTS

J. F., a 35 year old Negro male, was admitted with the complaint of daily chills for the preceding week. Except for the fact that he was a heroin addict the history was irrelevant. Physical examination revealed multiple abscesses of both upper extremities, a generalized erythematous rash and numerous petechiae. Although the initial examination of the heart revealed no abnormality, within several days a blowing systolic murmur was heard over the tricuspid area. This murmur persisted throughout the hospital course, but decreased in intensity as the patient improved. There were physical findings of consolidation over the right lung, and roentgenological examination was suggestive of pulmonary infarction. These findings disappeared after two weeks. In the interim, six blood cultures were reported positive for a *Staphylococcus aureus*. He was started on 200,000 units of penicillin by continuous intramuscular



infusion daily. After a few days, intermittent intramuscular injections of 20,000 units at two-hour intervals were substituted. He made an uneventful recovery after 56 days of treatment and was discharged after 108 days in the hospital.

One year later this patient returned with a history of pain in the left side of the chest and hemoptysis. In the meantime he had resumed the use of heroin. On admission there were signs of consolidation over the left lower lobe. A very faint systolic murmur was heard over the tricuspid area. This murmur was hardly audible and no change was noted during this hospital stay. The diagnosis was lobar pneumonia and he was placed on a regime consisting of 75,000 units of penicillin every three hours by mouth. There was no improvement after 72 hours of treatment and in the meantime a *Staphylococcus aureus* was twice grown from the blood. He was then given 500,000 units of penicillin per day by continuous intramuscular infusion. When the blood cultures remained positive and the resistance of the organism was found to have increased eight-fold the dose was increased to 1,000,000 units per day. In spite of these high doses the infection remained uncontrolled, and penicillin was discontinued after 10 days. Sulfadiazine was then given for four days without response. The organism was found to be sensitive to 0.22 unit per cubic centimeter of streptomycin and he was started on a course of 5,000 units every four hours by intermittent intramuscular injections. The fever subsided within two days and the course thereafter was uneventful. Streptomycin was administered continuously for 56 days.

*Comment.* This patient was of particular interest because he was apparently cured of acute endocarditis on his first admission, and returned one year later with clinical symptoms of bacteremia. He had in the meantime resumed the use of heroin by intravenous injection. The staphylococcus recovered on the second admission was different from the organism causing the previous infection, and therefore it is certain that this illness represented a reinfection rather than a recurrence. A definite diagnosis of acute endocarditis could not be made at this time because no change in the tricuspid murmur occurred and no new murmurs were heard. The high resistance to penicillin and low resistance to streptomycin of the organism causing the second infection was also of interest. While the patient continued to show signs of overwhelming infection during the administration of large doses of penicillin he made a remarkable clinical improvement within the first 24 hours after streptomycin was started.

L. M., a 38 year old Negro woman, was admitted with a history of cough, pain in the left side of the chest and chills. She was a heroin addict, although she denied having taken the drug for eight months prior to admission. Physical examination revealed evidence of consolidation over the left lower lobe. It was thought that the patient had pneumonia, and she was given 15,000 units of penicillin every three hours intramuscularly. On the second hospital day she developed bilateral thrombophlebitis in the lower extremities, and roentgenological evidence of pulmonary infarction. Both femoral veins were ligated.

The high incidence of bacteremia which has been observed in heroin addicts in this hospital<sup>16</sup> prompted us to take daily blood cultures. Three of these were positive for a *Staphylococcus albus*. On the ninth hospital day a blowing systolic murmur was heard over the tricuspid area. This murmur increased in intensity and persisted throughout the period of observation. At this time it was thought that the patient had acute endocarditis of the tricuspid valve. The initial dose of penicillin was not changed during the first three weeks of treatment because the patient showed clinical

improvement and the blood cultures remained sterile. On the twenty-second hospital day the patient developed fever, and the *Staphylococcus albus* was again cultured from the blood. The dose was increased to 50,000 units every two hours, since the resistance of the organism had increased four-fold. When the patient improved it was decided to maintain this dose. After one month on this regimen the patient again had an exacerbation of symptoms and the organism was again found on blood culture. The dose of penicillin was therefore increased to 2,000,000 units per day by continuous intramuscular infusion. A few days later this dose was reduced to 1,000,000 units when it was found that the resistance of the organism had increased only two-fold. The course thereafter included a bout of malaria which was treated successfully with atabrine. Treatment with penicillin was continued for 56 days following the last exacerbation.

*Comment.* This patient aroused much interest while under observation. Although she was a heroin addict, she denied the use of the drug intravenously for eight months prior to admission. This kind of history is usually unreliable, however, and it seems unlikely that an infection related to the use of heroin would have remained latent for eight months. On admission the question of whether the patient had pneumonia or pulmonary infarction arose, and from the subsequent course it was thought she had the latter. During each exacerbation she responded symptomatically to what proved to be inadequate doses of penicillin, and during each of these periods the resistance of the organism increased. Ultimately the dose of penicillin was increased sufficiently to control the infection.

A. S., a 38 year old Negro male, was admitted to the surgical ward with a history of having been ill for three weeks with chills, fever and pains in the chest and both thighs. Four days prior to admission he had developed abdominal pain. The remainder of the history, as given, was irrelevant. Physical examination revealed a temperature of 103° F. and pulse of 110. No abnormalities of the heart were found. Crepitant râles were heard over the base of the right lung posteriorly, direct and rebound abdominal tenderness was present over the right upper and lower quadrants, and there was exquisite tenderness of both thighs, more marked on the left. Although the patient had numerous scars over the veins of both forearms, on admission he denied the use of opiates by injection. Later, however, the patient admitted the use of heroin by intravenous injection. Roentgenological examinations of the chest, abdomen and thighs revealed no abnormalities. A tentative diagnosis of ruptured appendix with subdiaphragmatic abscess was made, and symptomatic and supportive measures were instituted.

There was no change in the patient's condition during the first 48 hours. At this time the patient was started on penicillin therapy, 20,000 units every three hours intramuscularly plus sulfadiazine by mouth, in doses of one gram every four hours following an initial dose of four grams. When this therapy had been continued for several days and no improvement had been noted, the sulfadiazine therapy was discontinued. The patient was then transferred to the medical service for further study. At this time treatment with penicillin was stopped also.

Another roentgen-ray examination of the chest revealed findings suggestive of pulmonary infarction. By the ninth hospital day a *Staphylococcus albus* had been cultured from two specimens of blood. At this time penicillin was resumed in doses of 20,000 units every two hours intramuscularly. The patient continued to have daily fever, however, and several days later the dose of penicillin was increased to 30,000 units every two hours. The remittent fever continued, nevertheless. The signs of

persistent infection and the experience of having found malaria previously in heroin addicts prompted us to look for malaria parasites. Blood smears were found to contain plasmodia, while repeated blood cultures with media containing penicillinase were sterile. The patient was then given a course of atabrine with prompt decline of the fever, following which the dose of penicillin was reduced to 20,000 units every two hours. During the third week and for the remainder of his hospital stay a harsh systolic murmur was heard over the tricuspid valve area. It was at this time that the diagnosis of acute tricuspid endocarditis was made. Penicillin was continued for 56 days.

*Comment.* This patient was of interest for several reasons. The bizarre symptoms and signs on admission obscured the diagnosis at first. The presence of malaria further confused the picture. Ultimately the diagnosis of acute endocarditis was established on the basis of the following facts: a history of the use of heroin by injection with unsterile instruments, positive blood cultures for a *Staphylococcus albus*, evidences of pulmonary infarction and the development of a persistent murmur over the tricuspid valve area. This patient demonstrates two of the complications of heroin addiction commonly seen in this hospital, acute endocarditis and malaria.

### DISCUSSION

Penicillin has materially altered the prognosis in acute endocarditis. Whereas formerly all patients with this disease died, an increasing number of reports of cases cured with penicillin are now being published. It has been stated that acute staphylococcic endocarditis results in the highest mortality, whereas in streptococcic and pneumococcic infections the prognosis is somewhat better.<sup>9</sup> We are unable to confirm this observation because all the infections in our patients with the exception of one were caused by the staphylococcus. Moreover, the three patients in our series who recovered had staphylococcic infections.

Analysis of the results of treatment in our series of patients fails to show any relationship between the duration of the infection before treatment was started and prognosis. It will be seen from table 2 that symptoms of the disease had been present for one to three weeks prior to admission in the three heroin addicts who recovered, whereas other patients who had been ill for only eight days died. In itself this observation suggests that these heroin addicts were able to combat the infection more effectively. Undoubtedly they inject some bacteria along with the heroin with the use of unsterile instruments, and consequently develop increasing resistance to infection. Furthermore, blood cultures were taken on all the heroin addicts on admission to the hospital, whereas they were not obtained on the other patients until the symptoms suggested the diagnosis of bacteremia or endocarditis. This practice led to the establishment of the diagnosis and institution of therapy before the disease became uncontrollable in the heroin addicts.

One has only to witness the fulminating course of a patient with acute endocarditis to be convinced that the only hope in this disease lies in early

diagnosis and vigorous treatment. Although the mortality in this group of cases is lower than in previously reported series, it is still extremely high. Analysis of the cases reveals that of the five patients who died, four probably were inadequately treated. The diagnosis was established late in the course of the disease in three of these patients so that penicillin had been administered for two days or less before death. In one patient there was such extensive involvement of the aortic and mitral valves that although he was treated for only one day, it is hard to believe that any amount of penicillin would have been of avail.

Whenever possible, the sensitivity of the causative organism should be determined and the dose of penicillin established accordingly. If the sensitivity of the organism to penicillin has not been determined, doses of 500,000 units per day should be given, since most cases of acute endocarditis are caused by staphylococci. These organisms are usually relatively resistant initially, or may easily develop resistance to penicillin, particularly when concentrations of the drug are inadequate.

The left side of the heart is predominantly involved in acute endocarditis. Staphylococci, streptococci and meningococci involve the mitral valve more frequently, whereas pneumococci and gonococci involve the aortic valve more commonly. When the right side of the heart is affected, it is usually at the tricuspid valve. The aortic and mitral valves were involved alone or in combination in four of the patients in this series. Pneumonia and pyelonephritis were the sources of infection in one each of two of these patients, and the source was undetermined in the other two. Since tricuspid endocarditis was found only in the four heroin addicts it is thought that this observation may be explained by the fact that the organisms were introduced directly into the veins and reached this valve first and in great numbers. There is apparently no significance to the observation that the three of the four patients with tricuspid valve involvement recovered, while the patients with lesions on the other valves died.

Although seven of the eight patients had evidence of embolic phenomena, only those patients with involvement of the tricuspid valve had pulmonary infarction. This is obviously explained by the anatomical relationship between this valve and the lungs. There were no deaths attributable to this complication.

#### SUMMARY AND CONCLUSIONS

1. Eight patients with acute endocarditis were treated with penicillin. Three with staphylococcic endocarditis recovered while four patients with staphylococcic and one with pneumococcic endocarditis died.

2. In the presence of symptoms of infection, the diagnosis of acute endocarditis should be entertained and repeated blood cultures taken. The usual acute fulminating course of this disease makes it mandatory that penicillin therapy be instituted early if success is to be achieved.

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Since this paper was submitted for publication two patients known to be heroin addicts with acute endocarditis have been treated successfully with penicillin.

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## CARDIAC ARRHYTHMIAS COMPLICATING TOTAL PNEUMONECTOMY \*

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THE surgical removal of the entire lung is the only method of treatment which has been employed to date that has been at all efficacious for pulmonary carcinoma. Many special problems attend removal of such a vital organ. Chief among the difficulties encountered is the effect on the heart and remaining lung of the abrupt shunting of the entire pulmonary circulation through the vascular bed of the one undisturbed lung. This fact takes on even more importance when one considers that there is probably no other part of the body, the derangements of which have such a profound influence upon the well being of man as those of the cardiovascular system. In addition it is important to point out that a disturbance of circulatory function suddenly developing will give rise to much more profound symptomatic effect than will one that develops insidiously over a prolonged period. In pneumonectomy, the disturbance is certainly precipitous.

The development of intrathoracic surgery was not accelerated until information accumulated regarding the various physiological factors that interfere with respiration and circulation when the chest is widely opened by the surgeon, and appropriate countermeasures became available to prevent or minimize these disturbances during and after operation. Once this was accomplished, other anatomic and technical details were developed for the operation of total pulmonary resection. One aspect, however, that has escaped sufficient attention until recently is the comparatively high incidence of dangerous cardiac arrhythmias following pneumonectomy and the resultant increased morbidity and mortality from the deteriorating effect of the arrhythmias upon the functional state of the heart. There is already abundant experimental and clinical evidence to indicate a profound immediate change in the electrocardiogram as a result of such procedures as pulmonary vessel ligation and lung collapse just prior to pneumonectomy. In animals, twisting of the lung hilus or incomplete clamping of the pulmonary artery has been shown to cause a negative effect upon the T-wave.<sup>1</sup> Krumbhaar<sup>2</sup> noted, following pulmonary artery ligation an increased amplitude of the P waves and frequent extreme ventricular deflections. Another group of workers<sup>3</sup> encountered five instances of transient cardiac arrhythmias in addition to T-wave changes following pneumonectomy in 11 dogs. In the past year, several clinical articles<sup>4,5</sup> have appeared calling attention

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to the occurrence of abnormal cardiac rhythms following thoracic surgery in humans. The present study was undertaken in order to determine the frequency with which cardiac arrhythmias have been encountered at Barnes Hospital following pneumonectomy and to attempt to discover the cause or precipitating factors that help initiate these arrhythmias.

## RESULTS

In an analysis of a series of 120 patients undergoing total lung resection, 11 or 9.1 per cent were found to have developed a detectable arrhythmia sufficient to have endangered the outcome of the operation or at least to have caused symptomatic difficulty. The operations were performed by Drs. Evarts A. Graham, Brian Blades, and J. Karl Poppe. The arrhythmias

TABLE I  
Incidence of Arrhythmias in Relation to Type of Pulmonary Lesion

Lesion	No. of Cases	No. of Arrhythmias	Per Cent
Bronchiogenic carcinoma	70	8	11.4
Mixed tumor	20	1	5.0
Bronchiectasis	11	2	18.2
Cystic disease	10	—	0.
Lung abscess	5	—	0.
Stricture of bronchus	2	—	0.
Fibrosarcoma ?	1	—	0.
Actinomycosis	1	—	0.
Total	120	11	9.1

included five instances of auricular fibrillation, four of auricular flutter and one each of frequent auricular and ventricular extrasystoles. As shown in table 1, the operations were performed for various types of pulmonary disease, the predominant one being bronchiogenic carcinoma. The right lung was removed in six of the patients developing postoperative arrhythmias and the left in five. Table 2 shows the location of the lesion with reference to

TABLE II  
Incidence of Arrhythmias in Relation to Location of Pulmonary Lesion

Lobe or Bronchus Involved	No. of Cases					
	Right Lung	No. of Arrhythmias	Per Cent	Left Lung	No. of Arrhythmias	Per Cent
Upper	20	2	10.	17	3	17.6
Lower	17	1	5.9	16	1	6.3
Middle	2	0	0.	—	—	—
Lower and Middle	3	2	66.6	—	—	—
Main	18	1	5.5	27	1	3.7
Total	60	6	10.	60	5	8.3

the lobes or bronchi involved. The type or location of the lesion had no specific relation to the occurrence of the arrhythmias, although abnormal cardiac rhythms did develop in two of the three patients with involvement of more than one lobe. Analysis of the presenting symptoms of the patients revealed the usual complaints of cough frequently associated with sputum, dyspnea, hemoptysis, weight loss, pain, fever, and weakness but no correlation could be detected between these symptoms and the subsequent development of cardiac disturbances.

All the patients developing arrhythmias were 35 years of age or older, the greatest incidence being between the ages of 40 and 70 years. Forty-two of the patients having a total pneumonectomy were under 35 years of age and actually 15 of these were children. Although of the total of 120 cases, 9.1 per cent developed abnormal cardiac rhythms, if we exclude the younger patients under 35 years from the group, the incidence percentage rises to 14.3 per cent. This difference is to be expected since the hearts of young

TABLE III  
Incidence of Arrhythmias in Relation to Age

Ages	No. of Cases	No. of Arrhythmias	Per Cent
1 to 10	11	—	0.
10 to 20	7	—	0.
20 to 30	16	—	0.
30 to 40	9	1	11.1
40 to 50	32	4	12.5
50 to 60	36	4	11.1
60 to 70	9	2	22.2
Total	120	11	9.1

people are generally in comparatively good condition and not prone to the development of cardiac accidents. Table 3 shows the number of cases and arrhythmia-occurrences in each age group.

In the total of 120 cases, mass ligation of the hilar structures was used in 29 patients with the development of cardiac arrhythmias in two instances (6.9 per cent), whereas the preferable individual ligation technic was used in the remaining 91 patients with nine abnormal rhythms developing (9.9 per cent). This difference hardly appears significant in this small group of cases. Of the patients developing arrhythmias postoperatively, eight were males and three females. From this sex difference, however, it is not to be concluded that these occurrences are more prevalent in men because three times as many males were operated upon as females. Study of the extent of the anemia before and after operation and the number of transfusions given the individual patients revealed that these factors had no influence upon the development of the cardiac abnormalities. Similarly no correlation was detected between febrile reactions and the cardiac disturbances encountered in



this study. Medications given prior to the development of the cardiac difficulties also presented no etiologic clue.

All the arrhythmias developed within one week after operation, one instance occurring on the second postoperative day, six on the third; two on the fourth, and one each on the sixth and seventh postoperative days. These time elements would indicate that the first seven days after operation are the ones which should be most carefully observed for the appearance of abnormal cardiac rhythms. The occurrence of arrhythmias apparently bore no relation to the development of other postoperative complications for whereas only four of the 11 patients with heart disturbances developed postoperative empyema and bronchial fistulae, slightly less than half of the others manifested these complications. Three of the patients with cardiac arrhythmias died and an extensive pericarditis was found in the two subjected to post-mortem examination. Occurrences of unusually rapid mediastinal shift appeared to bear no relationship to the incidence of abnormal cardiac rhythms. Since a previous report<sup>4</sup> suggested that vagal irritation from bronchial stump infection may precipitate the arrhythmias and since vagal stimulation has been shown to induce auricular fibrillation under certain conditions, consideration was given to the correlation of possible excessive vagus nerve manipulation or disturbance during or after operation with the occurrence of arrhythmias but no relationship could be discerned.

Twenty-six of the total group of 120 patients presented some evidence of heart involvement prior to operation either on physical or more frequently on electrocardiographic examination. Two of these patients actually had a diagnosis of right bundle branch block on their preoperative electrocardiograms. It is interesting to point out that only in one of these 26 cases was a detectable postoperative arrhythmia encountered whereas the remainder of the arrhythmias appeared in patients with presumably adequately functioning hearts preoperatively. Further study revealed that in addition to the 11 patients developing abnormal cardiac rhythms and symptoms therefrom, at least six other individuals showed some objective physical or electrocardiographic evidence of cardiac difficulty not present preoperatively. In this connection it is important to point out that total removal of a lung did not result in a single instance in the appearance of a coronary pattern in the electrocardiogram postoperatively. Careful study of this subject was stimulated by the fact that one of the patients, nine months following his pneumonectomy, developed a typical attack of coronary thrombosis associated with the usual electrocardiographic changes. After reviewing 31 cases in which electrocardiograms were available before and after operation, and following a special study of an additional 15 patients in which not only the routine but also fourth leads had been obtained before operation and upon discharge from the hospital, no instance was encountered of the development of a coronary pattern in the electrocardiogram as a result of the total lung removal. Furthermore, since so many of these patients are in the age group

where coronary accidents are prone to occur, such complications are to be expected without necessarily being connected with the previous operation of total lung resection.

#### CASE REPORTS OF NINE PATIENTS WITH POSTOPERATIVE AURICULAR FIBRILLATION OR AURICULAR FLUTTER

*Case 1.* L. D., a 63 year old white woman, had had a productive cough for the past eight years and fever for one year. Physical examination showed massive atelectasis of the right lung; bronchogram and bronchoscopy revealed a block of the right main stem bronchus. A diagnosis of mixed tumor of the right main bronchus was made and the patient had a total pneumonectomy with mass ligation of the hilar structures. Auricular fibrillation developed on the third postoperative day and in spite of digitalis treatment for five consecutive days, the patient died on the eighth postoperative day.

*Case 2.* M. W., a 48 year old woman, had had a productive cough for six months and weakness for three months. On physical examination she was found to have a massive atelectasis of the right lung. Bronchogram together with bronchoscopy revealed a block of the right main stem bronchus. A diagnosis of bronchiogenic carcinoma of the right main bronchus was made, and a total pneumonectomy was performed by individual ligation technic. Except for the development of auricular flutter on the fourth postoperative day the patient made an uneventful recovery. The arrhythmia disappeared without specific medication and the patient was discharged in good condition. When last heard from, three years after operation, she was in good health.

*Case 3.* W. T., a 46 year old man, was admitted to the chest service with a history of productive cough for one year and fever, pain, and hemoptysis for three months. Physical examination showed massive atelectasis of the left upper lobe and a bronchogram revealed a block of the left upper lobe bronchus. The diagnosis of a bronchiogenic carcinoma was made and a total pneumonectomy was performed (individual ligation). The patient's postoperative course was complicated by the development of an empyema, a bronchial fistula, pericarditis, and auricular fibrillation on the fourth postoperative day. The patient was given digitalis and quinidine sulfate with return to sinus rhythm. Subsequently auricular flutter developed transiently. The patient was finally discharged in only fair condition and, according to a communication from his family, died three months after operation from heart failure.

*Case 4.* H. W., a 44 year old male, was admitted with a history of productive cough and weight loss for one year and pain and dyspnea for four months. Physical examination showed a right upper lobe atelectasis and bronchogram revealed a block of the right upper lobe bronchus. The diagnosis of bronchiogenic carcinoma was made, and a total pneumonectomy was performed (individual ligation). The patient's postoperative course was complicated by the development of auricular flutter with 2:1 and 3:1 block on the third postoperative day and also by the development of an empyema. The arrhythmia disappeared without specific medication on the seventh postoperative day. The patient was discharged and when last contacted, one year later, was in good health.

*Case 5.* L. T., a 57 year old man, was admitted to chest service complaining of a productive cough, hemoptysis and weakness for one month. Physical examination and bronchoscopy showed a block of the left lower lobe bronchus. The diagnosis of bronchiogenic carcinoma was made and a total pneumonectomy was performed (individual ligation). The patient developed auricular flutter with 2:1 block on the third postoperative day. The arrhythmia after treatment with digitalis changed to

auricular fibrillation and finally to a sinus rhythm. When heard from four months after discharge the patient was in good condition.

*Case 6.* E. S., a 59 year old man, was admitted to chest service with right universal bronchiectasis which involved particularly the middle and lower lobes. A total pneumonectomy was performed by the individual ligation method. Postoperatively the patient developed an empyema and auricular flutter with 2:1 and 1:1 block on the second postoperative day and within two hours was in moribund condition with extreme heart failure. The cardiac glycoside, k-strophanthin, in the dose of 1.5 mg. was given in maintenance doses and reversion to sinus rhythm occurred on the fifth postoperative day. Later the patient was discharged in excellent condition without cardiac symptoms. He was seen again six months later and was found to be in good health.

*Case 7.* F. T., a 67 year old female, was admitted to the hospital with a history of dry cough, weakness and dyspnea for six months. Physical examination showed an atelectasis of the left upper lobe and bronchogram together with bronchoscopic examination revealed a block of the left upper lobe bronchus. A total pneumonectomy was performed (individual ligation). On the second postoperative day the patient developed auricular fibrillation which lasted for three days and disappeared without medication. The patient was discharged in excellent condition and at last report, two years later, was enjoying good health.

*Case 8.* L. H., a 53 year old man, was admitted to the hospital complaining of cough and hemoptysis for six months and dyspnea and weakness for three months. Physical examination showed an atelectasis of the left upper lobe and the bronchogram revealed a block of the left upper lobe bronchus. The diagnosis of bronchiogenic carcinoma was made and a total pneumonectomy was performed (individual ligation). The patient developed auricular fibrillation on the fifth postoperative day which did not improve in spite of digitalis administration for 17 days. The patient was discharged but returned to the hospital six months later with the auricular fibrillation still present. At this time digitalis was tried again with some improvement in his heart condition but the arrhythmia persisted.

*Case 9.* N. M., a 39 year old man, was admitted to chest service with a history of a productive cough and hemoptysis for seven months and weakness and weight loss for three months. Physical examination revealed an atelectasis of the middle and lower lobes on the right. Bronchoscopic examination showed a tumor mass extending into the right middle and lower lobe bronchi. The diagnosis of bronchiogenic carcinoma was made and a total pneumonectomy was performed (individual ligation). The patient made an uneventful recovery with the exception of the development of auricular fibrillation on the seventh postoperative day. At this time he was fully digitalized and two days later normal sinus rhythm was restored. The patient was discharged without any cardiac symptoms.

## DISCUSSION

The cause of the development of the arrhythmias following pneumonectomy remains obscure although precipitating factors appear to be involved in some of the cases. Age appears to be an important predisposing element with the older age group showing the higher incidence of this complication. Consideration of other possible associated etiologic and anatomic influences gives no direct clue as to why certain patients undergoing the arduous procedure of pneumonectomy do develop such cardiac disturbances and others do not. As is commonly known these arrhythmias may be precipitated by

any sudden effort, nervous excitement, trauma or surgical procedures. Fundamentally in the background there is always the potentiality of the individual's inherent physiologic nervous reactivity to these sudden stresses and strains initiating the mechanism leading to the production of the abnormal cardiac rhythms. In studying the natural history in the general population of the development of auricular fibrillation and auricular flutter which are the more important of the arrhythmias encountered in this study, usually one finds in the background definite evidence of heart disease, although sometimes the individual so affected may not present any detectable derangement. As stated previously, however, in this study no correlation was noted between prior heart involvement and subsequent cardiac abnormalities. Sudden compensatory emphysema in the remaining lung should be considered as a potential factor, in the production of the arrhythmias but against this possibility is the lack of evidence of a significant amount of post-operative emphysema developing, and the absence in the first place of any close association between emphysema and cardiac arrhythmias.

The most likely reason for the high incidence of arrhythmias following pneumonectomy has been suggested by an experimental study reported by Smith and Wilson.<sup>6</sup> They pointed out that an auricle which has been rendered irritable by anoxemia may be precipitated into fibrillation through the effect of vagus nerve stimulation shortening the refractory period of the auricle and lessening conductivity. From the clinical point of view there is a strong suggestion that in heart disease which is attended by reduced coronary artery flow and anoxemia of the myocardium, normal vagal stimuli might be amplified in their effects upon the heart, leading in some cases to the establishment of auricular arrhythmias. Certainly the common occurrence of auricular fibrillation in coronary artery disease, myocardial infarction and congestive heart failure is well known. From this and other clinical experimental evidence it appears very logical to conclude that the two factors of anoxemia and vagal stimulation act synergistically in the production of abnormal cardiac rhythms. In the procedure of total pneumonectomy a certain degree of anoxemia very likely occurs, although every attempt is made to reduce the extent of anoxemia by means of routine use of oxygen administration postoperatively. The factor of vagal stimulation occurs indirectly to a greater or smaller degree as a result of the extensive thoracic manipulation necessarily involved in total pneumonectomy.

In treating the patient who develops an arrhythmia, the physician and surgeon have to decide whether special treatment should be given to control the ventricular rate or whether it is preferable to wait for possible spontaneous reversion to a normal sinus rhythm as may occur in many instances simply with the help of morphine or other forms of sedation. This important decision must always be based on the condition of the patient since immediate specific therapy in serious cases may be either life saving or at least necessary to allay congestive heart failure. Rapid digitalization in

such instances is then indicated. In case there is imminent danger such as occurred in Case 6 where rapid auricular flutter resulted in profound cardiac failure after only a few hours, intravenous use of a cardiac glycoside such as lanatoside-C, or K-strophanthin may mean the difference between life and death. If there is no immediate danger, one may give either digitalis by the oral route, or quinidine sulfate, or even both depending upon the individual circumstances of the case. The important fact to point out, however, is that the patient's cardiac rhythm must be carefully and frequently observed during at least the first postoperative week in order to determine at the earliest possible moment the onset of abnormal heart action and thus permit early decision as to the therapeutic procedure of choice. In addition, since in such patients from whom a lung has been removed, breathing is loud and stertorous and the bronchial and tracheal noises usually sufficiently pronounced to drown out the cardiac sounds, it is advisable to take frequent postoperative electrocardiograms in order to check accurately the cardiac rhythm by objective means, to recognize a hitherto unsuspected auricular flutter, and to aid in the management of the patient once the arrhythmia has developed.

### SUMMARY

Arrhythmias are among the chief cardiac complications encountered following total pneumonectomy and occurred in 9.1 per cent of the entire series of 120 patients studied and in 14.3 per cent of those over 35 years of age. The arrhythmias included five instances of auricular fibrillation, four of auricular flutter and one each of frequent auricular and ventricular extrasystoles.

Apart from the factor of age, the reason for the high incidence of arrhythmias following pneumonectomy could not be definitely determined. It is suggested that anoxemia and vagal stimulation may act synergistically in the production of these abnormal cardiac rhythms.

Constant observation must be maintained for early recognition of the occurrence of abnormal cardiac rhythms. Treatment should be directed primarily to the attainment of prompt restoration of a normal sinus rhythm, and this result may be most often accomplished by rapid intravenous digitalization.

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# RHEUMATOID SPONDYLITIS: A STUDY OF 1,035 CASES \*

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STUDY of more than 1,000 cases of rheumatoid spondylitis encountered at the Mayo Clinic has yielded data which may help to clarify certain aspects of this disease and may help the physician to answer a few of the questions frequently asked concerning the condition. The erythrocyte sedimentation rate and the roentgenographic findings in cases of rheumatoid spondylitis also will be discussed briefly.

## SEX, AGE AT ONSET, SYMPTOMS AND COURSE

*What is the incidence of this disease in men as compared to women?* In our series there was a total of 931 men and 104 women. The ratio of men to women was 9:1. Seven hundred forty-nine patients had rheumatoid spondylitis without peripheral rheumatoid arthritis. There were 671 men and 78 women; a ratio of 9:1. Two hundred eighty-six patients had peripheral rheumatoid arthritis associated with rheumatoid spondylitis; 260 were men and 26 were women; a ratio of 10:1. These ratios are essentially the same as for the group as a whole.

*What is the age at onset in this disease?* The distribution of cases in this series according to the age at onset of symptoms is shown in table 1. Symptoms of 80 per cent of patients first appeared when they were between the ages of 15 and 35 years. The average age at the onset of symptoms in this series was 26.7 years. The age at the onset of symptoms in men and women did not show any significant variation from the average.

*What is the location of initial symptoms of rheumatoid spondylitis?* The first symptoms were most frequently in that part of the pelvis, lumbar and thoracic regions known as the torso (table 2). In about half of these cases (359 cases) the lower part of the back or lumbar region was specified. In 124 cases the onset of symptoms was in the region of the hip and in 100 the disease was first manifested by sciatica. The first symptoms were referable to the thoracic region in 60 cases and the specific part of the back could not be localized in 100. The first symptoms appeared in the neck and shoulder girdle in only 3.4 per cent of the cases (35 cases). These data seem to indicate that it is uncommon for symptoms of rheumatoid spondylitis to begin in the neck and only seldom do they begin in the thoracic region and pursue

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a descending course. In most of the cases then the spinal symptoms of the disease follow an ascending course; they begin in the lower part of the back and extend upward.

Symptoms in peripheral joints are sometimes an initial manifestation of rheumatoid spondylitis. They were found in 242 or 23 per cent of the cases in this series. The average age of these patients is slightly less than that of the group as a whole, 24.7 years as compared to 26.7 years. Symptoms referable to peripheral joints were polyarticular in 87 per cent of cases and monarticular in 13 per cent. There seemed to be a marked predilection for involvement of joints of the lower extremity in this phase of rheumatoid spondylitis. Joints of the lower extremities other than the hip were involved

TABLE I  
Age at Onset of  
Symptoms

Age, yrs.	Cases
Less than 20	244
20-29	518
30-39	170
40 or more	86
Total	1,018*

\* In 17 cases age at onset of symptoms was indeterminate.

TABLE II  
Location of First Symptoms

Torso		743
Lower back; lumbar region	359	
Hips	124	
Sciatic region	100	
Thoracic region	60	
Back, not localized	100	
Neck and shoulder		35
Peripheral joints		242
Miscellaneous		15
Total		1,035

in two thirds of the 242 cases (65 per cent). In most of the remaining cases (31 per cent) joints of both the upper and lower extremities were involved, and joints of the upper extremities alone were involved in 4 per cent of the cases. There was no apparent residual damage of the peripheral joints in 50 per cent of the 242 cases. Symptoms referable to peripheral joints at the onset of rheumatoid spondylitis did not predispose to involvement of peripheral joints later during the course of the disease.

*What is the course of the symptoms in rheumatoid spondylitis?* In 72 per cent of the cases studied exacerbations and remissions were a characteristic feature of the course of this disease. In 28 per cent a fulminating progressive course without any remissions occurred. This feature of the symptomatology is maintained regardless of the location of the initial symptoms.

*What is the predictable duration of the disease?* Unfortunately, this is a question which cannot be answered for an individual patient. The length



of time symptoms had been present prior to examination at the Mayo Clinic is shown in table 3. Symptoms had been present for 20 or more years in 74 cases. The average duration of symptoms prior to our examination was 8.5 years. This does not indicate the average duration of the disease by any means but it serves as a basis for evaluating certain features of the course of the disease as it occurred in this study.

*What is the possibility of the disease being limited to spinal involvement? or, What is the incidence of arthritis in special regions during the course of rheumatoid spondylitis?* Limitation of motion in the cervical portion of the spinal column was noted in 45 per cent of cases in this series after an average duration of symptoms of eight and one half years. Transitory symptoms in the region of the neck had been present in an additional 12 per cent of the cases. Involvement of the hip joints was noted in 28 per cent of

TABLE III  
Duration of Symptoms at  
Examination at  
Clinic

Years	Cases
Less than 5	311
5-9	242
10-14	201
15-19	90
20 or more	74
Total	1,018*

\* In 17 cases duration of symptoms was indeterminate.

cases. The joint damage was bilateral in three fourths of these cases. Arthritis of the hip and shoulder or the so-called root-joint involvement has at times been regarded as a characteristic feature of rheumatoid spondylitis. Although this association was noted in a fourth of the cases in this group, it occurred in only 7 per cent of all the cases studied. Patients having initial symptoms of rheumatoid spondylitis referable to the region of the hips showed no increased incidence of arthritis of the hip joints.

Involvement of peripheral joints producing residual damage of joints at the time of our examination was noted in 28 per cent of cases. Transitory symptoms were described in an additional 22 per cent of the cases. Thus, it might be said that symptoms referable to peripheral joints will occur in one half of the cases of rheumatoid spondylitis but in only a fourth of the cases will it lead to chronic, residual articular damage. When involvement of the peripheral joints does occur under these circumstances, the chances are it will be monarticular in a third of the cases.

## SEDIMENTATION RATE

Estimation of the sedimentation rate is a procedure frequently used as an aid in evaluating rheumatic symptoms. The sedimentation rate was less than 40 mm. in the first hour (Westergren method) in slightly less than half of the cases (table 4). In an additional 28 per cent it was from 40 to 59 mm. making about three fourths of the cases in which it was less than 60 mm. In the remaining cases the sedimentation rate varied from 60 to more than 100

TABLE IV  
Sedimentation Rate  
(Westergren Method)

Mm. in 1 hr.	Cases	Per Cent
Less than 20	176	19
20-39	254	27
40-59	264	28
60-79	133	14
80-99	79	8
100 and more	43	4
Total	949	100

mm. We wish to emphasize that the sedimentation rate was normal in 176 cases or nearly a fifth of the cases. It would seem that the sedimentation rate does not tend to be as high in rheumatoid spondylitis as it is in peripheral rheumatoid arthritis, although at times high readings may be seen in the former.

## ROENTGENOLOGIC MANIFESTATIONS

Roentgenologic evidence of rheumatoid spondylitis may be lacking if the progress of the disease has not resulted in destruction of cartilage and subchondral bone. When present, the characteristic roentgenologic findings in rheumatoid spondylitis are arthritis of the sacro-iliac and apophysial joints, calcification or ossification or both of spinal ligaments and osteoporosis of vertebrae. The so-called bamboo spine has in the past been regarded as the characteristic roentgenologic evidence of rheumatoid spondylitis but the changes seen in sacro-iliac joints are equally characteristic and occur much earlier.

Involvement of the sacro-iliac joints in rheumatoid spondylitis is typically bilateral. In this study bilateral sacro-iliac arthritis occurred in 98 per cent of the cases, an example of which is shown in figure 1a. The patient, a man 23 years of age, had had low back pain and sciatica which affected first one side and then the other for two years. Blurring and irregularity of the

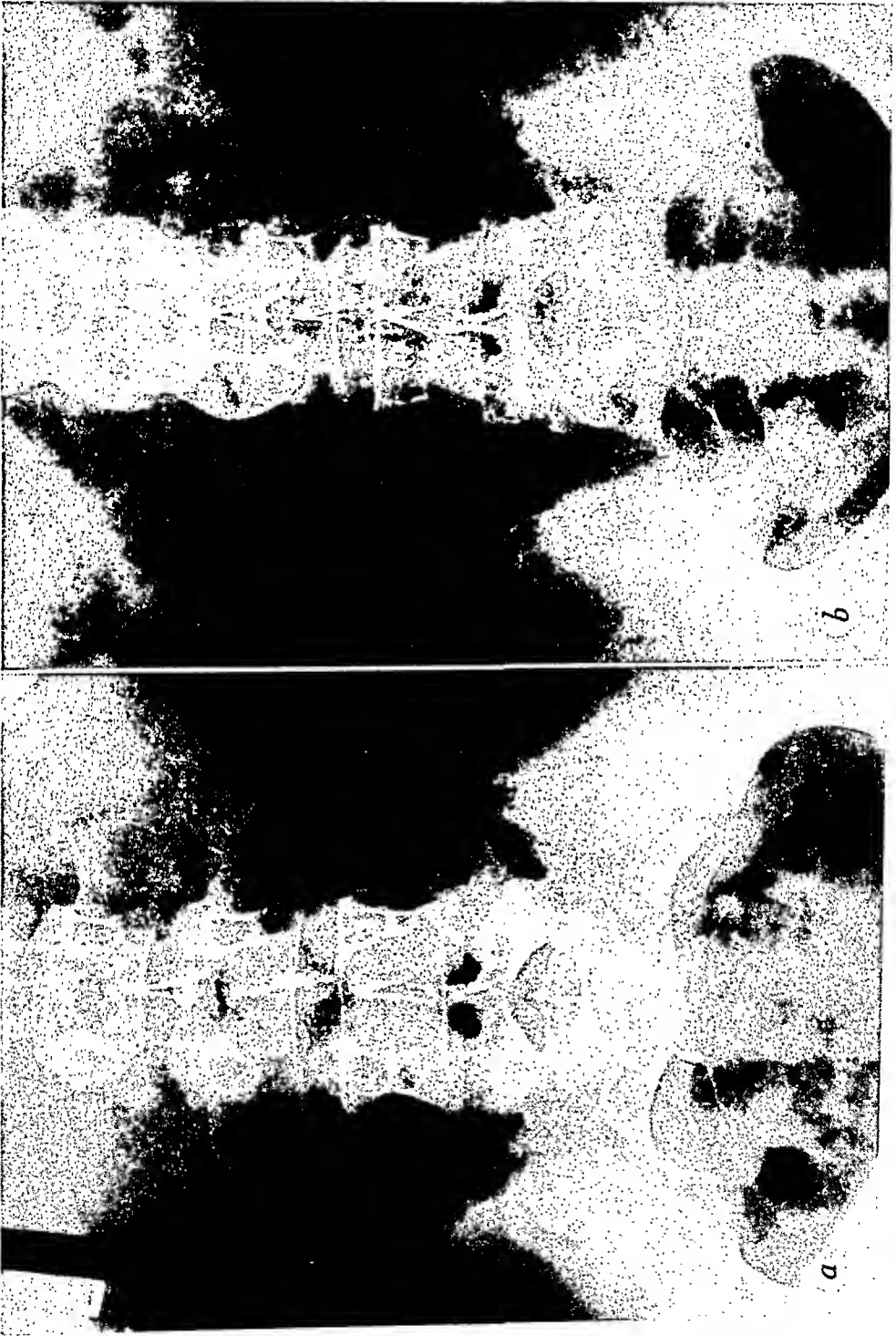


FIG. 1. Bilateral sacro-iliac arthritis characteristic of rheumatoid spondylitis; *a*, on first admission; *b*, 10 years later. There is evidence at this time of ligamentous calcification in the lumbar region. The sacro-iliac joints are nearly obliterated.



Fig. 2a. The lumbar portion of the spinal column in a case of rheumatoid spondylitis showing calcification of the anterior spinal ligament. This is to be contrasted with *b*. *b*. The osteophyte of osteo-arthritis in the lumbar part of the spinal column. See also figure 3 and text.

joint surface due to an actual destructive arthritis and marginal sclerosis of both sacro-iliac areas may be seen.

Arthritis of apophyseal joints undoubtedly occurs as a significant part of the disease process but it is often difficult to demonstrate roentgenologically. Calcification of spinal ligaments may be present at the time of the first symptoms but it is more often demonstrable only after months or years of the disease. It was not evident in the roentgenogram shown in figure 1*a* which was made when the patient was first seen. However, when he was reexamined 10 years later, after he had had symptoms for 12 to 13 years, the roentgenogram revealed the ligamentous calcification characteristic of rheumatoid spondylitis (figure 1*b*). The sacro-iliac joints were nearly obliterated.

The ligamentous changes seen in rheumatoid spondylitis are usually distinct and should not be confused with the changes of osteo-arthritis of the spinal column. A roentgenogram of the lumbar part of the spinal column in a case of rheumatoid spondylitis is shown in figure 2*a*. Calcification of

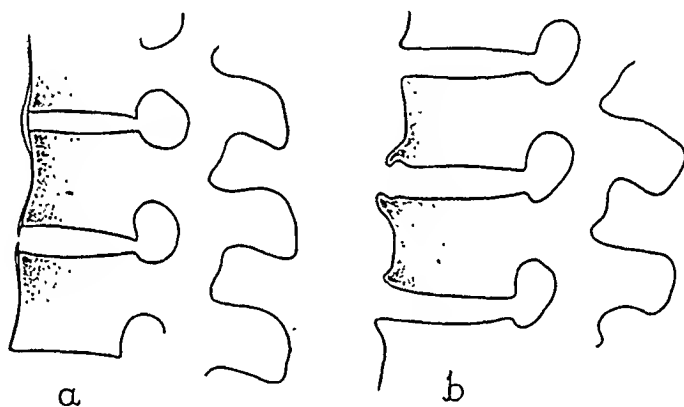


FIG. 3. Diagrammatic representation of roentgenograms shown in figure 2*a* and *b*.

the anterior longitudinal ligament is incomplete in one region but has progressed to bridging of two of the vertebrae in another region. A calcified spinal ligament is seen as a thickening of homogeneous density superimposed on the surface of the vertebra and spanning a normal intervertebral space. For comparison a roentgenogram of the lumbar vertebrae in a case of osteo-arthritis showing spur formation in several areas is included (figure 2*b*). The osteophyte has a variation in density, and cortex and cancellous bone may at times be as clearly differentiated as in the body of the vertebra.

The same conditions are diagrammatically represented in figure 3. Figure 3*b* shows the bony spur or osteophyte which is an outgrowth of the vertebral body; and figure 3*a* shows the calcified ligament, in close apposition to the vertebra but superimposed on it rather than being a part of it.

Unilateral sacro-iliac arthritis suggests the presence of a specific infectious disease, such as tuberculosis, but it may occur infrequently in rheu-

matoid spondylitis. It was noted in six cases in this study, an example of which is shown in figure 4. Symptoms of rheumatoid spondylitis had been present for 10 years before figure 4 was made. Marginal sclerosis and destruction of the right sacro-iliac joint but no apparent involvement of the left sacro-iliac joint may be noted in the roentgenogram. In the lumbar region there is marked evidence of calcification of spinal ligaments.



FIG. 4. Unilateral sacro-iliac arthritis in a patient who had had rheumatoid spondylitis for 10 years. Calcification of spinal ligaments in the lumbar region is marked.

Absence of roentgenologic evidence of involvement of the sacro-iliac joints is unusual in rheumatoid spondylitis but it does occur. It was found in nine cases in this study. In the case, the roentgenogram of which is included, symptoms of rheumatoid spondylitis had been present for seven years prior to examination at the clinic (figure 5a). In this case too, fusion of the laminae of the second, third, fourth and fifth cervical vertebrae occurred (figure 5b).

The negative or unilateral sacro-iliac joint changes which may be seen in cases of rheumatoid spondylitis, however, do not detract from the significance of the 98 per cent of cases in which the changes are bilateral. It is advisable



FIG. 5a. Absence of roentgenographic evidence of sacro-iliac arthritis in patient who had had rheumatoid spondylitis for seven years; *b*, fusion of the laminae of the second, third, fourth and fifth cervical vertebrae in same case as *a*.

to make roentgenograms of the sacro-iliac joints as well as the painful part of the spinal column in all cases in which rheumatoid spondylitis is considered in the differential diagnosis.

#### COMMENT

For at least some of the other questions which might be asked about rheumatoid spondylitis the answers are less easily obtained and perhaps less satisfactory. We hope that further study will produce more information of value to the understanding of this disease.



# TRICHINOSIS: REPORT OF AN EPIDEMIC \*

By FREDERICK H. HATHAWAY, Capt., M.C., A.U.S., and LAMSON BLANEY, Capt., M.C., A.U.S.

TRICHINOSIS is an acute disease usually occurring in man following the ingestion of pork products infested with the encysted larvae of the Nematode, *Trichinella spiralis*. The illness is characterized by fever, muscular pains, swollen eyelids, and a variable course, depending on the degree of infestation. The adult forms of the parasite (male and female) develop in the intestinal tract where the female deposits her eggs after penetrating the mucosa. In a few days the young *trichina* enter the intestinal lymphatics and are then transported by the circulatory system to all parts of the body. Usually, the initial symptoms of the disease are gastrointestinal and occur during the first week after ingestion of trichinous meat. Following this there is a period of toxicity corresponding with the migration of the larvae throughout the body. Finally, there is a period of larval encystment in muscle tissue during which time the patient either recovers from the disease or continues on to cachexia and death.

## REPORT OF THE EPIDEMIC

The present report is concerned primarily with 83 German prisoners of war who were hospitalized for trichinosis at an A.A.F. Regional Station Hospital. Their ages varied from 18 to 41 years with an average age for the group of 25.5 years. Eighty-two patients were admitted between Dec. 28, 1945 and Jan. 28, 1946. One patient, admitted on Dec. 19, 1945, with the diagnosis of cellulitis of the hand, later developed trichinosis (Jan. 1, 1946) in the hospital. One individual who had been transferred to the prison compound from another installation had his first meal in the prison mess on Dec. 20, 1945. This man noted initial symptoms of trichinosis on Jan. 15, 1946. The length of hospitalization for the entire group ranged from 19 to 48 days with an average hospital stay of 26 days.

All of these patients were members of a detachment of 587 prisoners confined in a nearby prison compound where they prepared and served their own food. The mess hall was opened on Dec. 4, 1945. The meat, which was supplied by the Quartermaster, was identical with that furnished troops stationed at the post. All meat used came from Federally inspected plants and in addition was inspected by the Veterinary Corps of the U. S. Army. This meat included raw pork sausage, supplied in the form of 10 lb. rolls, in quantities sufficient to last approximately two days. A check revealed that sausage was issued by the Quartermaster to the prisoners'

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mess only on the following dates: Dec. 6, 7, 9, 17, 19, and 26, 1945. On Dec. 28, 1945 a sufficient quantity was issued to last through Jan. 1, 1946. Sausage appeared on the menu at the prison mess approximately three times weekly and was usually served uncooked. Questioning of the patients revealed that the ingestion of raw pork is widely prevalent in Germany, especially in the northern portions. That this is a relatively safe practice there may be gathered from the statistics cited by Gould<sup>1</sup> which stated that the proportion of hogs with trichinous infection in Germany was approximately 0.001 per cent. In Berlin between the years of 1883 and 1924 no case of human trichinosis was reported after the eating of pork that had passed

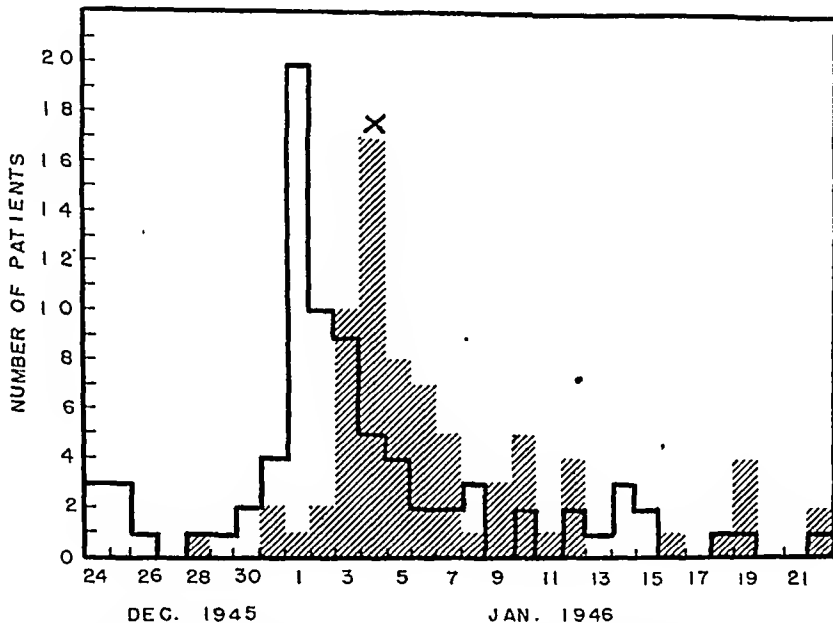


CHART 1. Solid line represents the date of onset of initial symptoms in 83 patients hospitalized with trichinosis. Shaded area represents the admission dates of 75 patients. (Two patients were admitted prior to December 24, 1945 for other conditions and subsequently developed trichinosis in the hospital. Six not included in chart were admitted between January 22 and 28, 1946.)

(X)—Indicates date after which no improperly prepared meat was served in the prison mess (Jan. 4, 1946).

microscopic inspection. In the United States, where the incidence of trichinosis in hogs is approximately 1.5 per cent, the individual is protected only by adequate cooking of all pork products.

The first few patients in this series were admitted to the hospital with a diagnosis of nasopharyngitis, sinusitis, and malaria. However, the presence of eosinophilia and swollen eyelids suggested that a more proper diagnosis was trichinosis. Steps were immediately taken to prevent any further serving of uncooked meat. Since these prisoners ate only food prepared in their own mess, with the exception of a few who occasionally ate at their place of work, there is no doubt that the source of infection in this epidemic was the uncooked sausage served during the month of December, 1945.

In this series the dates of onset ranged from Dec. 24, 1945 to Jan. 22, 1946 (chart 1). In explaining the rather wide spread of dates of onset several factors must be considered. First, it is improbable that all the pork eaten was trichinous; second, the amount eaten per man varied. Twelve men in this series gave a history of having eaten more than the "usual" amount. Some obtained second servings, while others who were kitchen workers ate double the "usual" amount. Third, gastrointestinal complaints as the initial symptoms occurred in only 29 individuals (34.9 per cent) and were mild in nature. Many were unaware of their illness until the onset of fever, swollen eyelids and headache.

### SYMPTOMATOLOGY

Symptoms of those individuals hospitalized were generally similar, varying only in degree of severity (table 1). All patients, at the onset of their illness, complained of fever, headache, and malaise. Headaches were of

TABLE I

Frequency of Symptoms as They Occurred in 83 Patients Hospitalized for Trichinosis

	Number	%
Total no. patients	83	
General symptoms		
Fever	83	100
101° or more	62	74.7
Less than 101°	21	25.3
Headache	83	100
Malaise	83	100
Muscle pain	77	92.8
Muscle pain with tenderness	48	57.8
Swollen eyelids	72	86.7
Dryness of mouth	54	65.1
Profuse sweating	38	45.8
Chills	10	12.1
Epistaxis	10	12.1
Diplopia	6	7.2
Gastrointestinal	29	34.9
Abdominal discomfort	14	16.9
Diarrhea	12	14.5
Nausea	6	7.2
Constipation	6	7.2
Vomiting	3	3.6

varying severity and duration, usually frontal in location, and most severe during the febrile period of the disease. In some individuals headaches persisted intermittently into convalescence. Moderate to severe malaise occurred in 55 (66.3 per cent) and lasted three to 30 days with an average of 15 days. The remainder (28 men) had mild malaise varying from two to 18 days with an average duration of nine days. Most of the patients remained in bed during the period their temperatures were higher than 100° F. Later, they tired easily with moderate activity on the ward and often

complained of excessive fatigue after performing ward "kitchen police." Nine patients still complained of mild fatigue at the time of discharge.

Swollen eyelids as seen on physical examination or reported in the history were noted in 72 or 86.7 per cent of the men hospitalized. Usually, the swelling subsided in three to five days.

Muscle pain was an outstanding complaint and occurred in 77 patients (92.8 per cent). Of this group 48 (57.8 per cent) had associated tenderness. Muscle pains were distributed roughly in the following areas: neck, upper extremities, lower extremities, and other areas; i.e., back, intercostals, abdominal, and ocular. It was found that 40 men (48.2 per cent) had pain involving three or more of these areas.

Profuse sweating, especially following any activity, occurred in 38 (45.8 per cent). Dryness of the mouth was a complaint in 54 men.

Chilliness was commonly associated with the onset of the disease and in 10 instances frank shaking chills were reported.

Recurrent epistaxis occurred in 10 men early in the disease. Diplopia coincident with swollen eyelids was reported by six patients.

Gastrointestinal complaints were not prominent in this epidemic. There were only three patients admitted primarily for this type of complaint. One of these patients was admitted for right lower quadrant pain which occurred 10 days after an episode of fever, swollen eyelids, and headache. A second had persistent nausea and vomiting. The third was admitted complaining of severe generalized abdominal pain and in addition had a temperature of 105° F. Histories taken on admission, however, revealed that gastrointestinal symptoms had occurred within the two-week period prior to admission in 29 (34.9 per cent). Of this number, 14 had had abdominal discomfort of varying degree and the remainder had noted diarrhea, constipation, or nausea with vomiting. Anorexia was a prominent feature in the entire series.

### PHYSICAL FINDINGS

The patients were all well nourished German prisoners of war who worked as laborers and translators. On admission none of the patients appeared seriously ill. The most significant physical finding was edema of the eyelids. Injection of the conjunctiva was present in 19 of the patients while hemorrhages of the bulbar conjunctiva were found in three, bilaterally in two and unilaterally in one. Examination of the fundi in all but four patients revealed only the incidental presence of a healed chorioretinitis in one and a congenital angioma of the left inferior temporal vein in another.

Lymph glands were palpable and often tender in 25 (30.1 per cent) of the patients. The finding varied from enlargement of a few posterior cervical glands in the majority to generalized lymphadenopathy of mild degree in four.

The spleen was palpable in four instances. One of these patients gave a

past history of malaria, another a history of infectious hepatitis in 1943. The spleen was tender in one of the remaining two.

An erythematous macular rash appeared in two patients. This faded the same day in one and recurred for several successive evenings in another. A few complained of transitory itching of the skin during the toxic phase. Two patients had firm, slightly tender, subcutaneous nodules measuring approximately 1 cm. in diameter which were present for about one day.

Mydriasis was noted in 15 patients (18.1 per cent). Their pupils measured more than 5 mm. in diameter early in the disease and returned to normal during convalescence.

Every patient in this series had a temperature higher than normal at some time during his illness. Sixty-two (74.7 per cent) had temperature elevations of 101° F. or higher and among these the highest recorded was 105° F. These temperatures were of a remittent type in 41 patients and of an intermittent type in 21. The duration of temperatures over 101° F. varied from one to 10 days with an average duration of one week. There was no significant difference in the height and duration of these two types of fever. These higher temperatures often were followed by the irregular, low grade, afternoon elevations which were common for the remaining 21 patients in this series. In some instances irregular, low grade, afternoon temperatures persisted for two to three weeks.

#### LABORATORY FINDINGS

During his hospital stay each patient averaged having 2.8 leukocyte counts and differential blood smears. Of the 83 patients hospitalized it was found that 69 or 83.1 per cent had leukocyte counts ranging higher than 10,000 per cu. mm. at some time during their illness. Of this number the highest counts recorded fell between 10,000 and 15,000 per cu. mm. in 52 patients (62.6 per cent); between 15,000 and 20,000 per cu. mm. in 13 patients; and above 20,000 per cu. mm. in five individuals. The highest count recorded was 28,000 per cu. mm. Finally, there was a group of 14 patients (16.9 per cent) whose white blood cell counts were always within normal limits (5,000 to 10,000).

In a total of 237 blood smears done on hospitalized patients it was found that 107 or 45 per cent showed eosinophilia ranging from 20 to 40 per cent inclusively. The other blood smears (130) showed eosinophilia of greater or lesser degree. The highest recorded eosinophilia was 61 per cent. No significant trend of eosinophilia was noted except for slightly lower counts in any given individual at the beginning and end of hospitalization. There was no relationship noted between the height of eosinophilia and the height of the leukocyte count.

The sedimentation rate in 70 patients was determined for the first time during the second and third weeks of illness and was repeated in several instances. The distribution of the highest sedimentation rate attained by

each patient was such that 41 (54.7 per cent) were within the normal range for males, i.e., 15 mm. per hour by the Westergren method. The sedimentation rates in 34 (45.3 per cent) were above that figure. Generally, the sedimentation rate returned to normal levels during convalescence in those patients showing elevated values.

TABLE II

Relationship of Eosinophilia to White Blood Count in a Representative Group (32) Selected from 83 Patients with Trichinosis. Week of Illness Calculated from Onset of Initial Subjective Symptoms

Case #	1st Week		2nd Week		3rd Week		4th Week		5th Week	
	W.B.C.	% Eosino- philia	W.B.C.	% Eosino- philia	W.B.C.	% Eosino- philia	W.B.C.	% Eosino- philia	W.B.C.	% Eosino- philia
1	7,000	1	9,950	36	9,100	4				
2			8,350	16			7,650	40		
3			7,000	55	8,850	26				
4	7,450	9	9,750	30	8,500	24				
5	9,100	0	9,400	26			9,700	14		
6	7,550	16	18,700	40			9,000	25		
7	7,300	1	11,500	50	8,500	25				
8	7,950	35	9,600	42	12,200	53				
9	11,700	53	14,150	39	14,500	41				
10	10,500	21	11,100	25	11,500	1				
11	12,000	24	7,400	30	6,050	35	8,800	23		
12	10,500	20	14,500	30	12,900	25				
13	10,400	34	6,800	26			12,600	29		
14	12,300	30	14,500	51					11,500	25
15	7,850	24	12,500	33			11,200	35		
16			8,500	25	12,350	40	11,900	38		
17	7,200	34	14,200	23			10,200	24		
18	7,800	30	13,500	25			10,100	25		
19	7,850	24	12,000	25	14,600	33				
20	6,300	18	9,350	29			11,550	39	11,050	25
21	7,200	11	12,750	38	10,950	28			10,950	15
22	5,250	10	9,850	39	11,400	17			4,800	2
23	9,500	24	10,650	39	12,350	37				
24	7,200	18	8,150	28					10,100	12
25	10,800	30	10,500	50			7,200	29		
26	9,850	40	11,150	36			7,400	27		
27	5,050	5	5,250	23	11,550	43	19,900	23		
28	11,400	0	16,450	20	16,400	18	11,200	25		
29	9,800	0	12,750	41			18,000	32	17,800	25
30	8,400	12	12,400	40	15,050	33			5,900	33
31	10,300	3	22,100	11	27,050	31	18,850	20	14,500	12
32			21,150	44	12,500	30	15,800	27		

In 14 cases a trace of albumin was found in the urine during the febrile period of the disease. In all but two of these the temperatures had reached 102° F. or higher.

The stools of several patients giving a history of diarrhea were examined, but in none were there significant findings.

#### SKIN TESTS

Intracutaneous skin tests were performed with a commercial type of Trichinella Extract (Eli Lilly & Co.) upon 80 patients (table 3). The

extract was a 1:10,000 dilution. The time of the test varied from five to 40 days after the onset of initial symptoms, 75 being performed on or after the thirteenth day of symptoms. The test site (volar aspect of forearm) was examined for an immediate positive skin reaction within less than 30 minutes after injection of the extract. The presence of a blanched wheal, larger than that produced by the initial injection was interpreted as an immediate positive reaction. This area was often surrounded by an area of erythema, but in no instance were pseudopods observed. There were 28 (34.6 per cent) immediate reactors. In nine of these a papule persisted for

TABLE III  
Results of Skin Tests Performed on 81 Patients with Trichinosis Using  
Commercial Trichinella Extract (1:10,000)

Total No. Tested—81			
Day of Illness	Imm. Pos. Reaction	Delayed Reaction	Negative Reaction
5th	1		
8th		2	1
11th		1	
12th		1	
13th	1	4	1
14th	2	6	
15th	5	11	1
16th	2	2	
17th	1		
18th	2	2	
19th	3		
20th	1	1	4
21st	2	1	1
22nd	2	4	1
23rd	1	1	1
24th	3	1	
25th		1	1
26th	1	1	
28th	1		1
36th		1	
40th			1
Total	28 (34.6%)	40 (49.4%)	13 (16%)

24 hours. Examination for a delayed reaction was made in 20 hours, at which time the presence of a red, slightly tender papule was regarded as positive. There were 40 (49.4 per cent) in this group. The remainder, or 13 (16 per cent) were negative. All control injections were negative. It is of interest to note that in one instance a test performed on the fifth day of illness resulted in an immediate reaction, but inasmuch as this man entered the hospital at a late date he probably became infected earlier than the onset of his symptoms would suggest. In a second, the test was negative when performed 40 days after the onset of symptoms of trichinosis. A third patient whose muscle biopsy was reported as showing interstitial myositis gave a negative reaction on the twentieth day of his disease.

## MUSCLE BIOPSIES

Muscle biopsies were performed in 10 patients (table 4). The ones selected were those who seemed to fall most closely into the typical clinical picture as seen in this series of 83 individuals. The site of biopsy was at the point of maximum muscle tenderness in each patient. A time interval of three weeks from the onset of initial subjective symptoms was allowed before the biopsy procedure.

TABLE IV  
Results of Muscle Biopsies in 10 Patients with Trichinosis Correlated with Their Respective Skin Tests

	Onset of Disease	Date of Biopsy	Site of Biopsy	Path. Findings	Results of Skin Tests
1	1/2/46	1/28/46	Biceps	Inter. myos.*	Imm. pos. react. on 19th day†
2	1/6/46	1/28/46	Gluteus max.	Inter. myos.	Imm. pos. react. on 15th day
3	1/2/46	1/28/46	Trapezius	Inter. myos.	Imm. pos. react. on 19th day
4	1/4/46	1/28/46	Biceps	Inter. myos. and larvae	Imm. pos. react. on 17th day
5	1/3/46	1/28/46	Gastrocnemius	Inter. myos.	Delayed react. on 25th day
6	1/1/46	1/28/46	Gastrocnemius	Inter. myos. and larvae	Imm. pos. react. on 20th day‡
7	1/8/46	1/28/46	Gastrocnemius	Inter. myos.	Negative on 20th day
8	1/3/46	1/28/46	Gastrocnemius	Inter. myos.	Imm. pos. react. on 18th day‡
9	1/3/46	1/28/46	Gastrocnemius	Inter. myos.	Delayed react. on 18th day
10	1/3/46	1/28/46	Gastrocnemius	Inter. myos.	Delayed react. on 18th day

\* Interstitial myositis.

† Immediate positive skin reaction and day of disease.

‡ Immediate positive reaction persisted as a papule for 24 hours.

The muscle biopsies were studied by serial sections of the entire blocks of tissue. The pathological report was similar in each of the 10 specimens, and was as follows: "Sections show varying degrees of interstitial myositis. The cells in the exudate are largely plasma cells, but there are also numerous eosinophiles. Occasionally, there is found a collection of such cells plus macrophages and giant cells, which have the appearance of foreign body granuloma. In addition to these inflammatory changes there are changes in the muscle as well. Single fibers show atrophy and less frequently hypertrophy. In the rare hypertrophic fibers there is usually seen hyperplasia of the nuclei." In addition to the above findings larval forms of *Trichinella spiralis* were found in two instances.

The results of skin tests in the 10 patients who had biopsies performed (table 4) revealed that six gave immediate positive skin reactions, three gave delayed reactions and one had a negative skin test on the twentieth day of his illness.



The average hospital stay of patients who had biopsies was 37 days. It was felt that the procedure prolonged their expected stay by seven to 10 days, especially those in whom the site of biopsy was the gastrocnemius muscle. The other laboratory findings in this group did not vary significantly from those of the other hospitalized patients.

### TREATMENT

Generally, treatment was symptomatic and supportive. Approximately 50 per cent of the patients received a saline laxative on admission but this did not alter their subsequent clinical course. One patient who was hospitalized on Dec. 19, 1945 for cellulitis of the hand received sulfadiazine, 1 gram every four hours, for four days (Dec. 19 to Dec. 23, 1945) and immediately following this a course of 300,000 units of penicillin was given over a period of 24 hours. However, on Jan. 1, 1946 he developed the symptoms of trichinosis which did not vary from the typical clinical picture observed in this series. A few other early admissions received sulfadiazine without demonstrable benefit. Another patient, who was hospitalized on Jan. 1, 1946 with a history of malaria, received atabrine in routine dosages for three days due to an erroneous laboratory report on his blood smear. This drug had no effect on his illness.

### COMPLICATIONS AND ASSOCIATED FINDINGS

At no time during their hospital stay were any patients considered seriously ill. No serious complications as a result of trichinosis were observed. Two individuals with complaints of abdominal pain were seen by the surgical consultant who felt that the complaints were associated with the primary disease, trichinosis.

Although headache of varying severity was present in every individual no meningeal signs or significant reflex changes were noted. One patient, on the tenth day of his illness, developed weakness of the right arm and leg with diminished pain sensation over the entire right side (midline distribution). Because there were no reflex changes noted and the condition cleared uneventfully in seven to 10 days it was felt that the episode was on the basis of a conversion reaction. Another patient had convulsive seizures which, after study by the psychiatric consultant, were said to be of an hysterical type. In one patient there was a recurrence of a rheumatoid arthritis which involved the left knee.

There were no cardiovascular complications noted. No deaths occurred in this epidemic. There were no patients hospitalized a second time for trichinosis during the two month period following the epidemic.

### STUDY OF GROUP NOT HOSPITALIZED

On Jan. 4, 1946 it became apparent that trichinosis was occurring in epidemic proportions. As previously stated, investigation revealed that

uncooked sausage had been served throughout December 1945. It was considered likely that each of the 587 prisoners had had an opportunity to ingest trichinous meat. Therefore, it was decided to obtain blood smears in order to ascertain the probable incidence of infection in this group as estimated by the degree of eosinophilia. The blood smears were taken on Jan. 10, 1946 while the prisoners attended evening mess. The men were divided into two groups, A and B (Chart 2). Group A was composed of

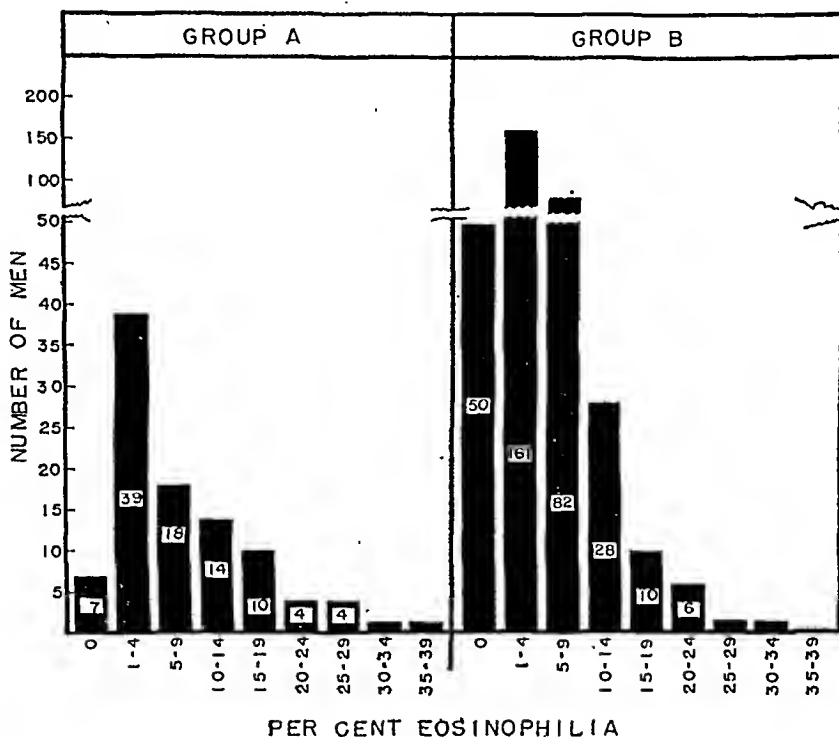


CHART 2. Results of blood smears for eosinophilia on 437 German prisoners of war (not hospitalized). The smears were taken on January 10, 1946 which was six days following the last improperly prepared meal in the prison mess.

Group A (98 men) was the symptomatic group.

Group B (339 men) was the asymptomatic group.

those individuals who during the previous two weeks had noted any of the following symptoms: fever, headache, malaise, muscular pain, or swollen eyelids—the symptomatic group. There were 98 blood smears taken in this group. Group B was composed of those men who felt as well as usual and had had no complaints during the previous two weeks—the asymptomatic group. There were 339 blood smears taken in this group. Twenty-four prisoners were admitted to the hospital between Jan. 10 and Jan. 28, 1946 and thus may have been included in either Group A or B. Of 528 prisoners who were confined to the compound on Jan. 10, 1946 blood smears were taken on 437 men or 82.8 per cent of the entire camp. The remaining 17.2 per cent were not available for study.

A study of the 437 blood smears (Group A and Group B) revealed a high number with eosinophilia present (Chart 2). Conclusions based on one series of differential blood smears, within one week of the last opportunity for infection, could not be considered accurate in determining the total incidence of infection in the compound because of the variable incubation period. However, for this series of blood smears the following arbitrary classification was established: Eosinophilia ranging from 0 to 4 per cent was accepted as within normal limits; eosinophilia ranging from 5 to 9 per cent was considered suggestive of trichinosis under the circumstances prevailing; eosinophilia ranging from 10 per cent to higher levels (36 per cent the highest) was considered as indicating that trichinosis was present. On the basis of this arbitrary classification it was found that 257 individuals or 58.8 per cent had an eosinophilia ranging from 0 to 4 per cent. One hundred (22.9 per cent) had an eosinophilia ranging from 5 to 9 per cent and these individuals were suspected of having trichinosis. Eighty men (18.3 per cent) had an eosinophilia of 10 per cent or greater and they were considered as actually having trichinosis at the time the blood smears were taken. On the basis of these findings it was felt that on Jan. 10, 1946 there were 139 prisoners who actually had trichinosis, 59 of whom had already been hospitalized. It is probable that in addition 100 others were infected (eosinophilia of 5 to 9 per cent). Further studies were not undertaken with this non-hospitalized group.

#### SUMMARY AND COMMENT

Trichinosis in epidemic proportions was studied in a group of 587 German prisoners of war. Eighty-three were observed in the hospital; 437 who were not hospitalized had blood smears taken (Jan. 10, 1946) approximately one week following the last improperly prepared meal in the prison mess. The presence of eosinophilia in a high percentage of the men not hospitalized suggested the presence of trichinosis in a mild or subclinical form in 100 individuals. On the basis of an eosinophilia of 10 per cent or greater, it was apparent that 80 men actually were infected regardless of the absence of symptoms.

This group of prisoners provided individuals whose activities were closely restricted. All food eaten necessarily came from one source (Quartermaster) and dates of issue of meat as well as amounts issued could be checked. It was known that the prison mess opened on Dec. 4, 1945 and that the first issue of sausage was on Dec. 6, 1945. It was also known that sausage was generally served uncooked. The exact date trichinous meat was served cannot be definitely determined. One patient hospitalized on Dec. 19, 1945 for cellulitis of the hand had initial subjective symptoms of trichinosis on Jan. 1, 1946, along with 19 other men who were not hospitalized at that time. This would suggest that trichinous meat was served on or before Dec. 19, 1945. Another patient, who was transferred into the

compound from a prison camp elsewhere on Dec. 20, 1945, developed initial symptoms of trichinosis on Jan. 15, 1946. It is assumed, therefore, that this man ate infected sausage at one or more meals between Dec. 20, 1945 and Jan. 4, 1946.

The question arises as to whether these men studied were infected prior to their arrival at this installation. It is possible, but with the evidence given and the explosive outbreak of initial symptoms of trichinosis occurring during the first three days of January 1946, it would appear that the source of infection was the uncooked sausage served during December 1945. In 1935 Drake,<sup>2</sup> et. al. reviewed trichinosis epidemics and reported an epidemic that occurred in Maine. It would appear that epidemics generally follow ingestion of improperly cooked sausage from hogs slaughtered on a small scale, and usually involve small groups. Ferenbaugh, et. al.<sup>3</sup> reported an epidemic of 64 cases occurring in a C.C.C. camp in Vermont in 1938. The source of that infection was meat from reliable packers which had had adequate inspection. It is of interest that the epidemic reported here also followed ingestion of meat from reliable packers. The danger of trichinosis is always present when improperly cooked pork is eaten, regardless of the source of the meat.

In this epidemic, which could be considered mild, the typical clinical picture was characterized by a sudden onset of chilliness, fever, malaise, and frontal headache. Associated with these complaints or occurring shortly afterward there was puffiness of the eyelids which generally lasted three to five days. In most instances muscle pain, or muscle pain with tenderness, occurred a few days later. In the typical case clinical muscle pain and tenderness had disappeared or diminished considerably at the time of discharge. Average hospital stay was 26 days. Gastrointestinal complaints, mild in degree, occurred as the initial symptom in less than half of the hospitalized cases.

It was observed that the peak of hospital admissions (17 patients) on Jan. 4, 1946 followed by three days the peak of onset of initial subjective symptoms (20 patients) on Jan. 1, 1946 (chart 1).

The outstanding physical findings were fever (remittent or intermittent in 65 patients) and swollen eyelids. Of the 77 patients who complained of muscle pain, associated tenderness was noted in 48.

The most significant laboratory finding was eosinophilia which ranged as high as 61 per cent. There was no constant relationship between the height of eosinophilia and the leukocyte count. However, at some time during hospitalization 69 patients had leukocytosis greater than 10,000 per cu. mm. Throughout this report the duration of illness has been calculated from the date of onset of initial subjective symptoms. Since it is generally accepted that eosinophilia does not usually appear during the week following ingestion of trichinous meat, it would appear from the high eosinophile counts obtained during the first week (table 2) that the patients were actually

farther along in the course of their disease than indicated. Clinical history, as given by the patient, was almost of equal importance in arriving at a diagnosis. However, this report has shown that patients with significant eosinophilia may have no complaints.

It is probable that many more persons in the group not hospitalized were infected than was evident from a study of their individual blood smears on only one occasion (Jan. 10, 1946).

The small number of muscle biopsies done (10 patients) provided valuable confirmatory information.

Skin tests were of value in diagnosis in 68 patients (84 per cent) of 81 patients in which they were performed.

No complications of trichinosis were observed in this series. No deaths occurred.

Based on studies up to and including Jan. 10, 1946 it is estimated that at least 139 prisoners were infected with trichinosis by that date. The presence of the disease was suspected in an additional 100 prisoners whose eosinophile counts ranged from 5 to 9 per cent on the date mentioned above.

### CONCLUSIONS

1. Trichinosis may occur in a mild form in epidemic proportions.
2. Trichinosis may occur in individuals without causing subjective complaints.
3. Eosinophilia, swollen eyelids (history or presence of), and positive skin test with trichinella extract are valuable aids in the diagnosis of trichinosis.
4. The height of the eosinophilia in mild trichinosis is not necessarily related to leukocytosis or the severity of the infection.
5. The sedimentation rate in mild trichinosis is usually within normal limits.
6. All pork products, regardless of the source, are potentially dangerous from the standpoint of trichinosis if served improperly cooked.

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# PLEUROPULMONARY TULAREMIA: OBSERVATIONS ON 12 CASES TREATED WITH STREPTOMYCIN \*

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IN the course of a study of streptomycin therapy of infectious diseases conducted at the Vanderbilt University Hospital and other hospitals in Nashville, the striking results which were obtained in the treatment of tularemia focused attention on this disease. These results were so impressive as to justify the conclusion that streptomycin treatment of tularemia is curative, in the strict sense of the word. The high incidence of tularemic pneumonia and the number of occasions in which the source of the infection was obscure and the diagnosis in doubt, suggested that this form of pneumonia is much more prevalent in this area than is generally recognized. Since tularemic pneumonia is a serious disease with a high mortality rate, its early recognition is a matter of the greatest importance in order that specific treatment may be begun without delay.

The primary pulmonic form of tularemia, as contrasted with pneumonia secondary to bacteremia and localization of *P. tularensis* in the lungs, is probably rare. Although this point is still a matter of debate, clinical evidence suggests that direct infection of the respiratory tract by inhalation of *P. tularensis* may occur, but that it is not a common method of infection. Pneumonia may occur in any of the clinical forms of tularemia. The commonly employed clinical division of tularemia into ulceroglandular, oculoglandular, and typhoidal types is somewhat arbitrary, and tends to fix the attention of the clinician upon the portal of entry of the infection rather than its systemic nature. The incidence of tularemic pneumonia is undoubtedly much greater than is suggested by the number of case reports. Stuart and Pullen<sup>1</sup> in a recent review of the reported cases of tularemic pneumonia in the United States could collect only 253, to which they added 15 of their own. Of these 268 cases, 97 (36.2 per cent) had neither demonstrable primary lesions nor enlargement of superficial lymph nodes and therefore conformed to the so-called typhoidal type of infection. This observation indicates clearly that in a large percentage of cases of tularemic pneumonia, there is no primary tularemic ulcer of the skin or mucous membranes.

The mortality rate of tularemic pneumonia as given by Blackford and Casey<sup>2</sup> in their excellent article on the clinical features of the disease, is in

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the neighborhood of 30 per cent. This figure may well be inexact, since the presence of pneumonia may be unrecognized in many mild infections and death may occur in severe infections before agglutinins against *P. tularensis* appear in the patient's serum. Nevertheless, it emphasizes the very serious nature of the infection.

It is now generally recognized that tularemia may be acquired by means other than the handling of tissues of infected wild rabbits and other wild rodents. The list of the known naturally infected vertebrate species in the report of Burroughs et al.<sup>3</sup> is impressive evidence of the large animal reservoir of the infection. The spread of the disease to man through the bites of certain blood sucking ticks and flies has been demonstrated. In the present series, several patients gave histories suggesting the possibility of transmission of the disease by ticks. Since the demonstration by Parker et al.<sup>4</sup> of the wood tick as a possible vector of tularemia, many cases of human infection have been reported in which ticks were suspected or proved as the transmitting agent. The most important tick vectors are apparently the wood tick (*Dermacentor andersoni*) and the common dog tick (*Dermacentor variabilis*).

#### STREPTOMYCIN IN THE TREATMENT OF TULAREMIA

*P. tularensis* has been shown to be highly susceptible to the action of streptomycin in vitro and experimental infections have responded promptly to treatment with the antibiotic.<sup>5</sup> The use of streptomycin in the treatment of human infections was first reported by Foshay and Pasternack.<sup>6</sup> These investigators observed a prompt clinical response in tularemia to the administration of comparatively small doses. Since the publication of this report, the remarkable response of tularemia to streptomycin treatment is rapidly becoming a common clinical experience. Foshay<sup>7</sup> has reported that the results of streptomycin treatment of tularemia as compared with those obtained with the use of hyperimmune serum are roughly comparable and that the therapy-to-recovery interval is not shortened significantly more by one agent than the other. However, he regards streptomycin as the agent of choice in the treatment of patients severely ill with tularemia.

#### ANALYSIS OF CLINICAL MATERIAL

During the period of the study of streptomycin therapy conducted in Nashville hospitals from April to September, 1946, 15 cases of pleuropulmonary tularemia were encountered. Twelve of these patients were treated with streptomycin. Eight of the 12 patients gave no history suggestive of a tularemic ulcer of the skin, and no primary lesions were found on physical examination. In two of the patients (Cases 1 and 3) the presence of pharyngeal ulcers and the occurrence of diarrhea during the early stages of the illness suggested the possibility of infection through the ingestion of infected

meat. Five patients gave a history of contact with wood or dog ticks and it was presumed that their infections were acquired in this manner, although proof of this hypothesis was not obtained. One patient had repeatedly killed and dressed wild rabbits but had no primary tularemic lesion.

Ten of the patients had bronchopneumonia, and in five of these pleural effusions were present. One patient had, in addition, acute pericarditis. There was one instance of tularemic lobar pneumonia. One patient had tularemic pleurisy with a small pleural effusion but no demonstrable pneumonia.

The diagnosis of tularemia was based on a rising serum agglutinin titer against *P. tularensis* and, in certain of the cases, was proved by the intraperitoneal inoculation of mice with sputum or pleural fluid and subsequent culture of the organism from the animals' spleens. Animal inoculation was carried out in 11 of the 12 cases by Dr. G. John Buddingh, Professor of Bacteriology at the Vanderbilt University School of Medicine, with positive results in seven cases. In vitro tests of the susceptibility of the isolated strains to the action of streptomycin were not carried out.

In 11 of the 12 cases streptomycin treatment resulted in dramatic clinical improvement. The one exception (Case 5) was an instance of tularemic bronchopneumonia with cerebral complications. Three patients were semicomatose and desperately ill at the time that they were treated with streptomycin. It is believed that treatment with the antibiotic saved their lives. There was a rise in the serum agglutinin titer in all of the patients during or after treatment with streptomycin. In several cases in which *P. tularensis* had been demonstrated in the sputum or pleural fluid by means of mouse inoculation before the institution of streptomycin therapy, inoculation of additional mice after therapy revealed that the organism had disappeared from these exudates.

One of the patients (Case 7) died suddenly after apparent recovery from tularemic bronchopneumonia. The cause of death appeared to be a massive pulmonary embolism. Permission for postmortem examination was not obtained. Seven of the 11 surviving patients were interviewed and examined at intervals of from one to five months after their discharge from the hospital. All had felt well since leaving the hospital and had resumed normal activity. In only one was there roentgen-ray evidence of residual pulmonary infiltration (Case 3). The original diagnosis in this case was tularemic lobar pneumonia. Roentgen-ray examination five months after the patient's discharge from the hospital revealed the persistence of patchy areas of infiltration in the involved lobe.

The course of the infection and its response to treatment with streptomycin as illustrated by these patients, is presented in tabular form (table 1). Certain of the cases which present features of special interest are reported in detail.



TABLE I  
Pleuropulmonary Tularemia  
Clinical Features and Response to Treatment with Streptomycin

Case	Patient	Diagnosis	Portal of Infection	Mouse Inoculation Before Treatment	Mouse Inoculation During or After Treatment	Serum Agglutinin Titer at Time of Treatment	Maximum Serum Agglutinin Titer	Maxi-mum W.B.C. (X1000)	Day of Illness on Which Treatment Started	Highest Tempera-ture on Day Treatment Started	Strepto-mycin Dosage (Intra-muscular)	Remarks and Clinical Result
1	W.H.S. 60 yrs. W.M.	Tularemia broncho-pneumonia with pleural effusion	? Oral (pharyngeal ulcers and diarrhea)	+(Sputum) on 14th day of illness	-(Sputum) on 19th day of illness	1:320	1:5,120	10.0	14th	104.2°	0.6 gram daily for six days	Semicomatose at the time treatment was begun. Marked subjective improvement. Cessation of diarrhea. Temperature fell rapidly and was normal after 4 days of treatment. Pleural fluid increased steadily during treatment.
2	L.R. 56 yrs. W.F.	Tularemia broncho-pneumonia with pleural effusion	Ulcer on left hand	+(Pleural) fluid on 14th day of illness	-(Pleural fluid) on 21st day of illness	1:640	1:5,120	10.2	16th	102°	0.6 gram daily for six days	Disappearance of symptoms within 24 hrs. Fall of temperature to normal values within 48 hrs. Slow healing of the primary ulcer and resolution of the pneumonia and pleural effusion over a period of 2 weeks.
3	S.H. 22 yrs. W.M.	Tularemia lobar pneumonia	? Oral (pharyngeal ulcers and diarrhea)	+(Sputum) on 13th and 14th days of illness	Not done	1:2,560	1:1,310,720	16.9	16th	102°	0.5 gram daily for five days	Symptoms disappeared within 24 hrs. Normal temperature after 3 days of treatment. No demonstrable resolution of the pneumonia after 3 weeks. Almost complete resolution after 5 mos. Marked rise in serum agglutinin titer following streptomycin treatment with subsequent fall to lower levels.
4	L.V. 28 yrs. W.M.	Tularemia conjunc-tivitis, broncho-pneumonia, pleural effusion and pericarditis	Multiple ulcers of left hand	+(Sputum) on 11th day of illness	-(Sputum) on 16th day of illness	0	1:40,960	8.6	11th	102.9°	1.0 gram for one day, 0.5 gram daily for 9 days	Patient semicomatose and desperately ill at the time treatment was started. Mentally clear, with marked subjective improvement, after 12 hrs. of treatment. Temperature fell steadily over a period of 1 wk. Persistent low grade fever during remainder of hospital stay. Rapid disappearance of pericardial friction rub. Slow resolution of the pneumonia and pleural effusion over a period of 2 weeks.
5	J.E. 67 yrs. W.M.	Tularemia broncho-pneumonia ? tularemia encephalitis	Ulcer of left hand	-(Sputum) on 8th day of illness	-(Sputum) on 10th day of illness	0	1:320	12.2	8th	103°	0.8 gram daily for 6 days, 1.6 grams daily for eight days	Slow fall in the temperature to normal values during a period of 5 days with partial resolution of the pneumonia and healing of the primary ulcer. Persistent stupor and headache, and secondary rise of temperature. Increased cell count in the spinal fluid. Apparent clinical response to larger doses of streptomycin.

TABLE I—Continued

Case	Patient	Diagnosis	Portal of Infection	Mouse Inoculation Before Treatment	Mouse Inoculation During or After Treatment	Serum Agglutinin Titer at Time of Treatment	Maximum Serum Agglutinin (X1000)	Day of Illness on Which Treatment Started	Highest Temperature on Day Treatment Started	Streptomycin Dosage (Intra-muscular)	Remarks and Clinical Result
6	C.B. 12 yrs. W.M.	Tularemia broncho-pneumonia ? tularemia wild encephalitis	Not known (history of skinning rabbits)	+(Sputum) on 40th day of illness	Not done	1:2,560	14.8	41st	100°	0.45 gram daily for six days	Patient not acutely ill at the time the treatment was begun and had only slight X-ray evidence of pneumonia. Striking mental confusion and bizarre behavior. Negative spinal fluid. Marked improvement in the mental status occurred after 2 days of treatment. Temperature slowly fell to normal values.
7	W.W. 35 yrs. W.M.	Tularemia broncho-pneumonia	Ulcer of right hand	+(Sputum) on 30th day of illness	Not done	1:640	9.0	31st	104.2°	1.0 gram for one day 0.5 gram daily for seven days	Marked clinical improvement within 24 hrs. after beginning of treatment. Temperature fell to normal after 3 days. Slow resolution of the pneumonia. Sudden death on the 7th day of treatment, apparently from a massive pulmonary embolism. No autopsy.
8	W.C. 23 yrs. W.M.	Tularemia broncho-pneumonia with pleural effusion	Unknown (? tick borne)	Not done	Not done	1:1,280	13.8	18th	103.8°	0.4 gram daily for seven days	Patient critically ill at the time treatment was begun. Definite clinical improvement within 24 hrs. and fall in temperature to normal values over a period of 4 days. Convalescence complicated by femoral thrombophlebitis. Almost complete resolution of pneumonia over a period of 3 weeks.
9	W.M. 30 yrs.	Tularemia broncho-pneumonia	Unknown (? tick borne)	Negative (Sputum) on 9th day of illness	Not done	1:320	13.4	10th	103.6°	1.0 gram for 1 day 0.5 gram daily for six days	Marked clinical improvement and a decline in fever within 24 hrs. Temperature fell to normal values over a 5 day period. Complete resolution of pneumonia after 3 wks.
10	H.H. 37 yrs. W.M.	Tularemia broncho-pneumonia with pleural effusion	Unknown (? tick borne)	+(Sputum) on 4th day of illness +(Pleural fluid) on 13th and 14th days of illness	+(Pleural fluid) on 17th day of illness	1:20	16.6	14th	104.2°	0.8 gram daily for four days 1.6 grams daily for three days	Patient semicomatose and desperately ill at the time treatment was begun. Definite clinical improvement within 24 hrs. Temperature fell steadily to normal levels over a period of one week. Resolution of pneumonia in 2 weeks. Residual pleural thickening.
11	J.C. 58 yrs. W.F.	Tularemia broncho-pneumonia	Unknown (? Tick borne)	-(Sputum) on 12th of illness	Not done	1:320	9.9	13th	102°	0.5 gram daily for six days	Subsidence of symptoms and fall of temperature to normal values within 36 hrs. Almost complete resolution of the pneumonia during a period of 1 week.
12	H.G. 36 yrs. W.M.	Tularemia pleurisy with pleural effusion	Unknown (? tick borne)	-(Sputum) on 6th day of illness	-(Pleural fluid) on 17th day of illness	0	10.0	14th	102°	0.5 gram daily for seven days	Patient had acute fibrinous pleurisy, and later developed a small pleural effusion. No serum agglutinins after 14 days of illness. Therapeutic trial with streptomycin resulted in a fall in the temperature to normal values. Agglutinins appeared in the serum. Convalescence complicated by the development of thrombophlebitis.

*Case 1.* (Chart 1) W. H. S. *Tularemic bronchopneumonia with pleural effusion.* This 60 year old white farmer was admitted to the Nashville General Hospital on April 22, 1946, on the service of Dr. R. E. Anderson. Two days before admission he had a severe chill followed by high sustained fever and marked prostration. He became irrational and markedly apathetic. No history of contact with wild rabbits or other rodents could be obtained except that during the week before the onset of illness he had eaten wild squirrels, which had been poorly cooked, on several occasions. He had had no contact with ticks.

On examination he appeared seriously ill. His temperature was 101.6° F. He was irrational and semistuporous. There were no ulcers of the skin and no significant enlargement of the superficial lymph nodes. There were two small, shallow, dirty ulcers on the pharyngeal pillars. Physical signs over the lower lobe of the right lung indicated an area of consolidation, and roentgen-ray examination confirmed the presence of bronchopneumonia. The spleen was not palpable. The leukocyte count was 6,800.

He was treated with penicillin without any effect on his illness. He continued to have high, irregular fever, with daily elevations as high as 105° and became more stuporous. On the fifth hospital day, he began to pass from 15 to 20 watery stools daily. No pathogenic organisms were cultured from the stools. On the eleventh hospital day, roentgen-ray examination of the chest revealed a small right pleural effusion. Serum agglutinins against *P. tularensis*, which had been negative on admission, were now reported positive in dilution of 1:320. A specimen of sputum was injected into mice. These animals died after five days and *P. tularensis* was cultured from scrapings of their spleens. Stool suspensions were rubbed into the shaved abdominal skin of other mice but no tularemic ulcers developed. Streptomycin (0.6 gram daily, given in divided doses intramuscularly at four hour intervals) was begun on the twelfth hospital day and the fourteenth day of illness. Within 24 hours he was markedly improved and was rational and alert. The diarrhea ceased. The temperature fell abruptly to lower values and within four days had become normal. Streptomycin treatment was continued for two additional days. The pleural effusion increased steadily in amount during treatment, but animal inoculation with both sputum and pleural fluid on the nineteenth day of the illness was negative. The pharyngeal ulcers healed slowly. The serum agglutinin titer rose to 1:5120. On the last day of streptomycin therapy, right thoracentesis was performed to relieve slight respiratory embarrassment and 1,000 c.c. of serosanguineous fluid were removed. Mice were inoculated with this fluid with negative results. At the time of discharge, the patient felt well although a roentgenogram revealed the persistence of a small amount of fluid in the right pleural cavity.

*Comment:* In this patient the presence of pharyngeal ulcers and the occurrence of severe diarrhea during the early stages of his illness suggested the possibility of an oral portal of infection. The diagnosis of tularemia was suspected but was not confirmed by serum agglutination tests until the eleventh day of illness, at a time when the patient was critically ill. Streptomycin treatment resulted in prompt clinical improvement. The marked subjective improvement and the abrupt cessation of diarrhea before the temperature had fallen to normal values were striking.

*Case 4.* (Chart 2) L. V. *Tularemic conjunctivitis, pneumonia, pleural effusion, and pericarditis.* A 28 year old white farmer was admitted to the Vanderbilt University Hospital on May 29, 1946. About two weeks before admission he had skinned a wild rabbit and had cut his hand. Ten days before admission multiple ulcers ap-

peared on his left hand and at approximately the same time he developed high fever and severe headache and malaise. Three days later he developed a cough which was productive of yellow sputum.

At the time of admission to the hospital he was critically ill. His temperature was 102.6° F. He was semicomatose and delirious. He coughed frequently, producing moderate amounts of tenacious yellow sputum. There was moderate dyspnea but cyanosis was not striking. There was a purulent left conjunctivitis. On the fingers of the left hand were three small shallow ulcers with indurated black margins. The left epitrochlear lymph node was enlarged and tender and there were subcutaneous nodules along the medial aspect of the left forearm. The left posterior cervical lymph nodes were moderately enlarged and tender. There were physical signs of a large left pleural effusion. A loud pericardial friction rub was audible. The spleen was felt at the costal margin. The leukocyte count was 4,600. Roentgen-ray examination of the chest confirmed the presence of a large left pleural effusion.

Before the administration of streptomycin a specimen of sputum was injected into mice. These animals died after five days and *P. tularensis* was cultured from scrapings of their spleens. No agglutinins against *P. tularensis* were demonstrated in the patient's serum. One gram of streptomycin was given intramuscularly during the first 24 hours. Thereafter, 0.5 gram was given daily. Twelve hours after the beginning of this treatment there was marked clinical improvement, although the temperature remained at high levels. He became rational and alert and dyspnea diminished. Within 48 hours the temperature had declined markedly and there was striking improvement in the appearance of the local lesions. The conjunctivitis had entirely cleared and the left epitrochlear and cervical nodes were smaller and less tender. He coughed less frequently and the sputum became mucoid. The pericardial friction rub disappeared, and no pericardial effusion developed. On the fourth hospital day, left thoracentesis was performed and 1,250 c.c. of serosanguineous fluid were removed. Specimens of the pleural fluid and of sputum obtained on the same day were injected intraperitoneally into mice but the animals survived. Following the removal of the pleural fluid there were physical signs over the left lower lobe indicating areas of consolidation, but upon subsequent roentgen-ray examination of the chest the residual pleural fluid obscured the lung fields. Streptomycin treatment was continued for a total of 11 days because of the persistence of low grade fever. There was progressive healing of the ulcers of the hand and decrease in the size of the lymph nodes. Physical and roentgen-ray examination of the chest revealed a decrease in the pleural effusion, although at the time of discharge on June 20 there was still a moderate amount of fluid in the left pleural cavity. The serum agglutinin titer rose steadily to 1:40,960. On examination two months later he was found to have some residual pleural thickening but no pleural fluid. He felt well and was at work on his farm. The serum agglutinin titer was 1:20,480.

*Comment:* The diagnosis in this case was obvious, although it is of interest that there were no serum agglutinins against *P. tularensis* on admission after 11 days of illness. The serum agglutinin titer rose rapidly and to high levels after streptomycin treatment. The response to streptomycin treatment was striking.

*Case 5.* (Chart 3) J. E. *Tularemic bronchopneumonia* (?), *tularemic encephalitis*. This 67 year old white farmer was admitted to the St. Thomas Hospital on July 7, 1946 on the service of Dr. B. H. Webster. Two weeks before admission, he had skinned a wild rabbit which had been caught by his dog. Five days before admission an ulcer appeared on his left thumb, and he had a shaking chill. He developed a severe headache and the following day had pleuritic pain in his right chest

and a non-productive cough. High fever and intense headache continued, and he became markedly prostrated.

The temperature at the time of his admission to the hospital was 102°. He was semistuporous but responded to questions and complained of severe headache. There was an indurated ulcer on the left thumb. The left epitrochlear and axillary lymph nodes were enlarged and tender. There were many fine moist râles over both lung fields, and a roentgenogram of the chest revealed diffuse bilateral bronchopneumonia. The leukocyte count was 10,600.

During the next few days he ran a high irregular fever and appeared acutely ill. His stupor deepened, and he became incontinent of urine and feces. A bilaterally positive Babinski sign appeared. Treatment with penicillin was ineffective. No agglutinins against *P. tularensis* were demonstrated in the serum. A specimen of sputum was injected intraperitoneally into mice, but the animals survived. Streptomycin treatment was begun on the third hospital day in doses of 0.8 gram daily, given intramuscularly in divided doses at four hour intervals. The temperature fell to normal over a period of five days, and definite clearing of the pneumonia was demonstrated by roentgen-ray examination. The ulcer of the left thumb began to heal. However, the patient continued to be stuporous and his temperature again rose, reaching a level of 102.4°. A lumbar puncture on the ninth hospital day yielded clear spinal fluid under normal pressure. The fluid contained 29 leukocytes per cu. mm., the majority of which were granulocytes. The protein content was 20 mg. per 100 c.c. Since the possibility existed that the cerebral process was tularemic, the dose of streptomycin was doubled. Within 48 hours after the dose of streptomycin had been increased, the patient showed marked clinical improvement. He was mentally alert and was free of headache. Serum agglutinins against *P. tularensis* were demonstrated for the first time on the fifteenth day of illness, in titer of 1:40. Streptomycin was continued for an additional week, a total of two weeks treatment. There was a gradual fall in the temperature to normal values. The Babinski signs disappeared. The serum agglutinin titer rose to 1:320. On the eighteenth hospital day the lumbar puncture was repeated. The fluid contained 2 leukocytes per cu. mm., and its protein content was 60 mg. per 100 c.c. The patient was discharged on the twenty-first hospital day, afebrile and clinically well.

When seen six weeks later, he felt well. There were no physical signs of pulmonary consolidation. The serum agglutinin titer was 1:320.

*Comment:* This case is presented in detail since the response to streptomycin was by no means as striking as that observed in the other patients. The diagnosis of tularemic pneumonia was not proved by the demonstration of the organism in the sputum. However, the appearance of serum agglutinins against *P. tularensis* after treatment with streptomycin supported the clinical diagnosis. The rise in agglutinin titer was not as rapid nor as marked as that observed in the majority of the patients in this series after streptomycin treatment. It is of interest that agglutinins were not demonstrated until the dose of streptomycin had been increased. The nature of the cerebral complication was not clear. The clinical picture and the improvement following larger doses of streptomycin suggest that tularemic lesions may have been present in the brain.

*Case 10.* (Chart 4) H. H. *Tularemic bronchopneumonia with pleural effusion.* A 37 year old white business man was admitted to the Vanderbilt University Hospital on July 21, 1946, on the service of Dr. Robert M. Finks. Ten days before admission

he developed high fever and pleuritic pain in the right chest. Physical examination of the chest was negative, but he was treated by his physician with sulfathiazole on the assumption that he had pneumonia. He continued to have high fever and became progressively worse. He developed a cough productive of moderate amounts of mucopurulent sputum. Sulfathiazole was discontinued, and penicillin and sulfadiazine were administered without any effect on the illness. On the sixth day of his illness fine râles and a friction rub were heard over the base of the right lung. During the next few days he became dyspneic and moderately cyanotic. Because of the failure of his pneumonia to respond to treatment with penicillin and sulfadiazine, he was referred to the hospital. He gave no history of contact with wild rodents. He lived in suburban Nashville in a region rather heavily infested with ticks and had removed wood ticks from dogs on numerous occasions. He had worn rubber gloves and recalled no tick bites.

On physical examination at the time of admission he appeared acutely ill. His temperature was 103.2° F. He was dyspneic, cyanotic, and mentally confused. There were no skin lesions and no enlargement of the superficial lymph nodes. The percussion note over the right chest was dull below the level of the sixth rib. Tactile and vocal fremitus were diminished in this area, and the breath sounds were suppressed and bronchovesicular in character. Many fine moist râles were audible over the area of dullness. The spleen was not palpable. The leukocyte count was 16,000. A roentgenogram of the chest revealed an area of consolidation in the right hilar region and a moderate amount of fluid in the right pleural cavity.

Under observation in the hospital irregular fever continued with daily rises as high as 104.2° F. The patient's condition became progressively worse in spite of treatment with penicillin and sulfadiazine. On the third hospital day right thoracentesis yielded 60 c.c. of grossly bloody fluid. The fluid contained 12,000 leukocytes per cu. mm. and cultures were sterile. He became more stuporous and on the following day was semicomatose and appeared desperately ill. A serum agglutinin titer against *P. tularensis* of 1:20 was reported. A second right thoracentesis yielded 450 c.c. of dark, bloody pleural fluid. A therapeutic trial with streptomycin was decided upon. Before the administration of streptomycin a specimen of sputum was obtained, and this, together with the specimens of pleural fluid, was injected intraperitoneally into mice. All of the mice subsequently died, and *P. tularensis* was cultured from their spleens. Streptomycin treatment was begun in doses of 0.8 gram daily given intramuscularly in divided doses at four hour intervals. The following day the temperature was somewhat lower, and the patient's mental state was clearer. On the second day of treatment the temperature had fallen to even lower levels. He was mentally alert, and there was marked decrease in the dyspnea and cyanosis. Right thoracentesis was performed on the fourth day of treatment and 450 c.c. of bloody fluid were removed. This fluid was injected into mice. The mice died after four days, and *P. tularensis* was again cultured from the splenic scrapings. Although this result was not immediately available to the clinician, the dose of streptomycin was doubled after three days of treatment because the patient's response was not as dramatic as had been anticipated. Progressive improvement continued, and the temperature fell steadily to normal levels. Treatment was continued for a total of seven days. Right thoracentesis on the fifth and nineteenth days of illness yielded 410 c.c. of blood-tinged fluid, but on the twenty-second day of illness only 15 c.c. of fluid could be obtained. Animals inoculated with these specimens survived. Roentgen-ray examination of the chest showed considerable clearing of the right lung field but some pleural thickening. The serum agglutinin titer rose progressively to 1:2,560. The patient was discharged on the eighteenth hospital day. When seen one month later he felt well. Fluoroscopic examination of the chest showed residual pleural thickening. The serum agglutinin titer was 1:1,280.

*Comment:* This patient had no primary tularemic lesion. The history of contact with dog ticks suggested that he might have acquired his infection in this manner. He was critically ill at the time treatment with streptomycin was instituted and it is believed that it saved his life. The diagnosis of tularemic pneumonia had not been confirmed definitely by laboratory studies, and streptomycin administration was in the nature of a therapeutic trial. The dose of streptomycin was increased in an effort to determine whether larger amounts of the antibiotic would result in a more striking clinical response. This seemed to be the case. The smaller doses may well have effected cure of the infection, but in this connection it is noteworthy that *P. tularensis* was recovered from the pleural field on the fourth day of treatment with these doses. The rapid rise in the serum agglutinin titer against *P. tularensis* after the institution of streptomycin treatment has been observed in the majority of the patients in the present series.

*Case 12.* (Chart 5) H. G. *Acute tularemic pleurisy.* This 36 year old white farmer and woodcutter was admitted to the Vanderbilt University Hospital on August 18, 1946. His illness began suddenly two days before admission with a shaking chill, followed by high fever and sharp epigastric pain. The pain was quite severe for about an hour and then subsided, leaving him with a continuous dull ache in the same area. Coughing, moving or straining caused marked discomfort. He gave no history of any contact with wild rodents, but during his work as a woodcutter he had repeatedly removed wood ticks from his skin. The ticks had not embedded themselves and he had noticed no ulcers.

On physical examination he appeared acutely ill. His temperature was 102° F. There were no ulcers of the skin or mucous membranes. The superficial lymph nodes were not enlarged. The lungs were clear to auscultation. There were marked tenderness and voluntary spasm of the upper abdomen bilaterally. The spleen was felt one finger's breadth below the costal margin. The leukocyte count was 6,100.

The patient ran a high irregular fever during his first week in the hospital. His epigastric pain and tenderness subsided within 24 hours, but on the day after admission he developed pleuritic pain in the left chest and a pleural friction rub was audible. A roentgen-ray of the chest revealed clear lung fields. On the fifth hospital day there were physical signs suggesting the presence of a left pleural effusion, and the patient raised small amounts of mucopurulent sputum. Mice were inoculated intraperitoneally with sputum, with negative results. Another roentgenogram of the chest revealed no evidence of a pleural effusion. Left thoracentesis was performed, but no fluid could be obtained. A third roentgenogram of the chest on the ninth hospital day showed a small pneumothorax, presumably resulting from the previous thoracentesis, but no pleural fluid. The patient was now free of pleural pain, his temperature had fallen to somewhat lower values, and he had no complaints except for moderate malaise and weakness. No serum agglutinins against *P. tularensis* were demonstrable on the third, seventh, and twelfth hospital days. On the twelfth hospital day, and the fourteenth day of illness, streptomycin treatment was begun as a therapeutic trial. Streptomycin was administered in doses of 0.5 gram daily in divided doses at four hour intervals. Within 24 hours his malaise had disappeared and he said that he felt perfectly well. The temperature slowly fell to normal levels over a period of four days. On the fifteenth hospital day, fluoroscopy of the chest revealed a small left pleural effusion. Left thoracentesis was done the following day and 8 c.c. of straw colored fluid were removed and injected into mice. The mice survived. On the following day, the seventeenth day of illness, agglutinins against *P. tularensis* were demonstrated in the serum for the first time, in a titer of 1:160. During the next week

there was a progressive rise in the serum agglutinin titer to 1:640. The pleural effusion gradually disappeared. Convalescence was complicated by the development of a left femoral thrombophlebitis associated with low grade fever and considerable swelling of the leg. Recovery was complete after a period of eight days. He was discharged on the thirty-first hospital day. At this time the serum agglutinin titer had risen to 1:5,120.

*Comment:* The diagnosis of tularemic pleurisy, without detectable pneumonia and with only a small pleural effusion, seems to have been established in this patient. He was treated with streptomycin solely as a therapeutic trial since laboratory confirmation of the diagnosis had not been obtained. The patient was not seriously ill at the time that treatment was instituted but exhibited a convincing clinical response to streptomycin.

## DISCUSSION

### *Observations on the Response of Tularemic Pneumonia to Treatment with Streptomycin*

Certain features in the response of these patients to streptomycin treatment seem worthy of comment.

*Subsidence of Symptoms Following Treatment.* In all of the patients obvious clinical improvement and subsidence of the constitutional symptoms—headache, aching in the extremities, mental lethargy or stupor, and prostration—occurred before the fall of temperature to normal values.

*Temperature Response.* In the patients with high fever at the time treatment was begun, the temperature usually declined within 24 hours, but in many instances it did not reach normal values until several days had elapsed.

*Disappearance of P. tularensis, from Exudates.* The results of animal inoculation of sputum or pleural fluid seemed to support the clinical impression that streptomycin treatment resulted in a rapid elimination of *P. tularensis* from the lesions of the lungs and pleura. In several instances, in which the organism had been demonstrated in sputum or pleural fluid by mouse inoculation prior to the institution of streptomycin treatment, additional mice were inoculated in an attempt to demonstrate the rapidity with which it was eliminated from these exudates and, by inference, from the tissues. The organism was recovered in only one instance after the institution of streptomycin treatment (Case 10). This patient was critically ill at the time that he was treated with streptomycin and *P. tularensis* was recovered from the pleural fluid on the fourth day of treatment. Animal inoculation of specimens of pleural fluid obtained subsequently was negative.

*Regression of Lesions.* In contrast to the marked clinical improvement which was observed, there was comparatively slow resolution of the pulmonary consolidations and pleural effusions, reduction in the size of the regional lymph nodes, and healing of the primary tularemic ulcers. The resolution and healing of these lesions were felt to have been accelerated somewhat by streptomycin treatment, although complete healing usually was not evident for several weeks.



*Effect of Streptomycin on the Immune Response.* The effect of streptomycin treatment on the immune response of the patient with tularemia is a subject of considerable interest. It was considered possible that early treatment with the antibiotic might prevent the development of acquired immunity and expose the individual to the danger of reinfection. None of the patients in the present series was treated within the first week of illness. However, in all of them, even those who had no demonstrable serum agglutinin or agglutinins in low titer at the time of treatment, a rise in titer occurred following streptomycin therapy. In several patients this rise was pronounced and rapid, suggesting that the destruction of large numbers of organisms had provided a marked antigenic stimulus. It is not known at present whether streptomycin treatment of tularemia will have any effect on the length of persistence of serum agglutinins. In six of the seven patients who were studied after an interval of several months, the serum agglutinin titer was either unchanged or only slightly lower than at the time of discharge from the hospital. One patient (Case 3) whose serum agglutinin titer rose to the remarkable level of 1:1,310,720 had a titer of only 1:1,280 five months after discharge from the hospital.

*Dosage.* Comparatively small doses of streptomycin were employed. Since the first patients in the series were treated with as little as 0.5 gram of streptomycin daily and showed a favorable clinical response, subsequent patients were given comparable doses. No instance of relapse of the infection was observed. These doses are smaller than those recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council in its recent report on the use of streptomycin in the treatment of infectious diseases.<sup>8</sup> The use of larger doses of the antibiotic in the treatment of severe infections is probably advisable. The evidence presented in this report indicates that the small doses of streptomycin which were employed cured the infection. However, larger doses of the antibiotic might conceivably have produced a more rapid response. In addition, the possibility of the acquisition of resistance by *P. tularensis* to the action of streptomycin exists, although no instance of this development has been reported. In all of the patients in the present series, streptomycin was injected intramuscularly in divided doses at four hour intervals. Streptomycin was not injected intrapleurally in patients with pleural effusions.

### *The Frequency of Tularemic Pneumonia and the Importance of Early Diagnosis and Treatment*

Study of this group of patients suggests that the frequency of tularemic pneumonia and pleurisy in central Tennessee, an area in which the tularemia is endemic, is probably much greater than is generally recognized. Since the incidence of human infections may be, in part, a reflection of the prevalence of the infection in the animal reservoir, it is possible that the apparent high incidence of severe tularemia with pneumonia may have resulted from an unusually high infection rate among native wild rodents. This

possibility was not investigated by field studies. Similarly, the number of cases in which tick transmission of the disease was a possibility may have been influenced by the season of the year in which the study was carried out. Even with these reservations, it would appear that tularemic pneumonia is by no means uncommon in this area and that it is unrecognized in many instances. This statement may also apply to other endemic areas in the United States. In three patients in this series a clinical diagnosis of severe atypical pneumonia, probably of viral origin, had been made at the time of their admission to the hospital. Our experience strongly indicates that at least one factor favoring recognition of tularemic pneumonia is the stimulus provided by the availability of a specific therapeutic agent.

The difficulties inherent in the laboratory confirmation of the diagnosis of tularemia were apparent in this study. It is important to recognize that during the early stages of the infection current methods may be of little value. The macroscopic serum agglutination test is usually relied upon for verification of clinical diagnosis. Although this test is extremely reliable, it is never positive during the first week of illness and, occasionally, agglutinins may not appear in the serum until the third or, rarely, the fourth week of illness.<sup>9</sup> This test is therefore unsatisfactory as an early diagnostic procedure. Isolation of *P. tularensis* from exudates by means of animal inoculation is hazardous for laboratory workers. Moreover, from four to seven days usually elapse before the animal dies and the infecting organism can be identified by stained smears or cultures. The intradermal test of Foshay,<sup>10</sup> in which a killed bacterial suspension is used as the test solution, is said to be highly specific. Intradermal tests were not employed in this study and their value in early diagnosis cannot be assessed.

Since the clinical diagnosis of tularemic pneumonia is frequently difficult and the commonly employed laboratory methods are not of great value in the early stages of the illness, a therapeutic test with streptomycin is a valuable diagnostic aid and has the great advantage of instituting specific treatment for the infection, which is usually severe and often lethal, without unnecessary delay. The rise in the serum agglutinin titer against *P. tularensis* which occurs during or after streptomycin treatment provides further confirmation of the diagnosis. Streptomycin was administered to two patients in this series as a therapeutic test. In one patient (Case 10), the serum agglutinin titer at the time of treatment was 1:20, and in the other patient (Case 12) there were no agglutinins in the serum after two weeks of illness. Both of these patients responded promptly and in one of them (Case 10) streptomycin was judged to have been lifesaving. In this case, *P. tularensis* was subsequently isolated from mice injected with sputum and pleural fluid before the institution of treatment. On the basis of the clinical data presented here, the administration of 1 to 2 grams of streptomycin daily for two days is suggested as an adequate therapeutic test. If clinical improvement occurs the antibiotic should be administered for a longer period.

## SUMMARY AND CONCLUSIONS

Streptomycin was used in the treatment of 11 cases of tularemic pneumonia and one case of tularemic pleurisy. The patients showed a prompt clinical response to small doses of the antibiotic. The rapid disappearance of *P. tularensis* from the sputum or pleural fluid, as determined by animal inoculation, indicated that the organism was rapidly killed in the tissues. The regression of pulmonic lesions and the healing of primary ulcers were believed to have been accelerated by streptomycin treatment but required a longer time interval than did clinical recovery. In all of the patients a rise in serum agglutinin titer occurred after treatment and in certain instances was very marked and rapid. This increase in the serum agglutinin level may have resulted from the antigenic stimulus provided by the destruction of large numbers of organisms.

The incidence of tularemic pneumonia during the period of study was striking. Because of the diagnostic difficulties presented by many cases of tularemic pneumonia and the prompt response of tularemia to streptomycin therapy, the value of a therapeutic trial with this antibiotic in severe pneumonia of undetermined origin in areas in which tularemia is endemic is apparent. In those cases which are due to *P. tularensis* withholding streptomycin in order to confirm the diagnosis by laboratory methods may, on occasion, endanger life. A dosage of 1 or 2 grams daily for two days is suggested as an adequate therapeutic trial in such patients.

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# CASE REPORTS

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## STEVENS-JOHNSON SYNDROME, A VARIATION OF ERYTHEMA MULTIFORME EXSUDATIVUM (HEBRA): A REPORT OF TWO CASES \*

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Two cases are presented—the first a syndrome of ulceromembranous stomatitis, purulent conjunctivitis, urethritis, and signs of constitutional toxicity; the second an eruptive bullous type febrile disease associated with stomatitis and ophthalmia. Both cases conform to the picture described by Stevens and Johnson. Stevens and Johnson<sup>3</sup> in 1922 felt that their syndrome of an eruptive febrile disease associated with stomatitis and purulent conjunctivitis was a distinct clinical entity. Controversy exists, however, as to whether the syndrome should be differentiated from erythema multiforme exsudativum.

Fletcher and Harris<sup>1</sup> in 1945 and Keil<sup>2</sup> in 1940 have presented excellent historical reviews. Erythemas were first described in 1808 by Willan and Bateman; Alibert and Bazin were the first to note an erythema-like skin rash in association with conjunctivitis and stomatitis in 1822; membranous conjunctivitis with skin rash was described in 1855; in 1866 von Hebra described *erythema exsudativum multiforme*; French investigators in 1917 described necrotic pseudo-membranous excoriating mucous membrane lesions involving the mouth, eyes, genitalia, vagina and rectum either without or with multiform erythematous skin lesions.

The two cases presented were admitted 18 days apart. They were similar, except for the fact that the one did not have an erythema multiforme-like skin rash. It seems likely that all such cases belong in the *erythema multiforme exsudativum* group which has been described so well by Fletcher and Harris,<sup>1</sup> and Keil,<sup>2</sup> and further defined by Koke.<sup>4</sup>

### CASE REPORTS

*Case 1.* D. Y., 37 year old white male, was referred to the Lancaster General Hospital on November 21, 1945, as a case of an unexplained oral mucous membrane lesion of two days' duration. Four days before admission he developed extreme malaise and drowsiness, aches and pains in his joints and back, fever and profuse night sweats, and cough with slight expectoration. Two days before admission he developed blisters under the upper lip followed by sore throat with difficulty in eating and swallowing. Excessive lacrimation had been present for two days. Burning on urination had been present for one day.

The family history was non-contributory. The general health had been good except that two years previously blisters had appeared in his mouth on one occasion but this was of short duration.

On physical examination the temperature was 103.2° F., pulse 100 per minute, and respirations 20 per minute. The patient appeared acutely ill, but oriented and con-

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operative. The skin was dry and no eruption was present. The conjunctivae were markedly hyperemic, and a purulent exudate was present. The ear drums and canals were normal and there was no nasal obstruction. The lips were swollen and ulcerated and the mucous membranes of the palate and gums were ulcerated, the ulcers being covered by a confluent membranous exudate; the tongue was swollen and covered by a membranous exudate; a foul odor was present. The nasopharynx was reddened and a few small ulcers were present. The submaxillary lymph nodes were enlarged bilaterally. Examination of the chest revealed increased bronchovesicular sounds in the left hilar area and a few musical râles throughout the chest. The examination of the heart was negative. Blood pressure was 130 mm. Hg systolic and 70 mm. Hg diastolic. The abdomen and extremities were normal. Reflexes were normal.

Laboratory findings were as follows:

Date	Hgb.	W.B.C.	Polys.	Lymphs.	Monos.	Eos.
11/21/45	92%	23,800	93%	7%	—	—
11/24/45	92%	8,900	65%	33%	1%	1%
11/27/45	79%	10,800	60%	39%	1%	—
11/30/45	—	15,000	—	—	—	—
12/ 7/45	79%	10,500	69%	27%	2%	2%

Urinalyses revealed a 1 plus albumin on two occasions and on November 22, 1945 there were a moderate number of finely and coarsely granular casts and a few hyaline casts present. On November 25, 1945 there was a 1 plus albumin but no casts were present. The Wassermann test was negative. Blood cultures on the second hospital day and the twelfth hospital day were negative. Smears from the mouth showed the following: gram positive cocci in pairs and chains, large and small gram negative rods (*N. catarrhalis*), no fusospirochetal organisms, and no *C. diphtheriae*. Cultures from the mouth showed hemolytic streptococci, *N. catarrhalis*, pneumococcus; negative for fungi. An anaerobic culture showed gram positive cocci in chains. Eye smears and cultures revealed *Staphylococcus albus*, diphtheroid bacilli, and *N. catarrhalis*. Smear and culture from the membrane over the urethra showed *Staphylococcus albus*; the pathological report was "fibrinopurulent membrane." Heterophile antibody test was positive in dilutions of 1:28. The Widal and the brucella agglutination tests were negative. Prothrombin time was 17 seconds. Platelet count was 599,400. Bleeding time was one minute and the coagulation rate was six minutes.

Roentgenogram of the chest on November 23, 1945 showed some infiltration in the left base and the right cardiohepatic angle, due to some stage of bronchopneumonia. Hilar shadows on the left side were exaggerated and contained one to two moderate sized glands. On December 3, 1945 a roentgenogram of the chest showed decrease in the pneumonic infiltration in both lungs with improvement especially apparent in the left. There was slight infiltration about the lower bronchi on both sides. Glandular enlargement in the hilus was not so pronounced.

Two days after admission there was some decrease in the inflammation of the mucous membrane lesion of the mouth and pharynx. There was increased cervical gland involvement and a violent ophthalmia was present. Three days after admission the patient complained of burning on urination and later of an inability to void; a tenacious membrane was removed from the urethral orifice and voiding occurred. This recurred two days later. His status on the fourth day after admission was (1) generalized toxicity, (2) ulcerative membranous stomatitis, (3) purulent ophthalmia, (4) membranous lesion over mouth of urethra, (5) albuminuria and casts, (6) bronchopneumonia, (7) nose bleeding, and (8) polymorphonuclear leukocytosis.

Constant improvement occurred from the seventh hospital day on. The membrane sloughed from the mucous membrane of the mouth leaving a raw ulcerated

surface. He was discharged on the twentieth hospital day with mild injection of the conjunctivae and with a small amount of membrane remaining on the soft palate.

He received 2,000 c.c. of 5 per cent glucose in normal saline intravenously on the day of admission. Penicillin, 20,000 units every three hours intramuscularly, was administered from the day of admission until the seventeenth hospital day. Ascorbic acid 100 mg. twice daily, and nicotinic acid 100 mg. twice daily by mouth; and Bejectal, 2 c.c., twice daily hypodermically, were administered during the hospital stay. Zinc sulfathiazole ointment, 5 per cent, was applied three times daily to the eyes. Penicillin paste was applied to the mouth and gums three times daily. Sodium perborate and diluted hydrogen peroxide mouth washes were used locally.

One month after discharge he complained of a burning sensation of the eyes at times, numbness at the end of the tongue, impairment of taste, abdominal pains between meals, and a burning feeling on defecation. A mild conjunctivitis was present but physical examination was otherwise normal. A barium enema was negative.

*Case 2.* A boy, age 11, entered the Lancaster General Hospital on December 7, 1945, complaining of sore mouth, sore eyes, and a rash on the hands and feet. Five days before admission his eyes had become inflamed. They watered considerably, and he complained that light hurt them. The day before admission the mouth and lips became sore. The same day a vesicular rash was noticed on one foot. On the day of admission the hands and feet were covered with this eruption as well as some spots on the arms and legs. A cough had been present for two days.

The family history was non-contributory except for diabetes in the maternal grandmother. The patient had had chickenpox, mumps, measles, tonsillectomy and adenoidectomy in childhood. At the age of five he had shown a faint trace of sugar in the urine, at which time he was put on a diet restricting starches and sweets for a year. There was no history of allergy to foods or pollens.

On physical examination the patient was acutely ill with a temperature of 103° F., pulse rate 120 per minute, and respiratory rate 28 per minute on the day of admission. Red vesicles and bullae were scattered over the face, hands, feet, and a few over the body. Smaller skin blebs resembled those of chickenpox. There was a good vaccination scar on the left arm. Eye examination showed a marked swelling of the lids with a serous discharge which had caked in slight yellowish crusts in the lashes. The conjunctivae were congested but showed no lesions similar to those in the mouth. There was congestion of the nasal mucous membranes. The ears were normal. The lips were covered with a grayish necrotic crust which covered ulcerated areas. Similar lesions involved the mucous membrane of the entire mouth, gums, and tongue. The pharynx was red and inflamed. There was bilateral cervical adenopathy most pronounced on the left side. Numerous coarse râles were heard anteriorly and posteriorly over the entire chest. The heart was normal. The abdomen was normal. The extremities were normal except for the skin lesions.

Laboratory findings were:

Date	Hgb.	R.B.C.	W.B.C.	Polys.	Lymphs.	Monos.	Eos.
12/ 9/45	79%	4,160,000	9,100	75%	22%	1%	2%
12/18/45	79%	3,930,000	9,800	58%	42%		

Several urinalyses were normal. Sedimentation rate on Dec. 18, 1945 was 17 mm. in one hour (Westergren). Smears from the eyes showed no definite organism; subculture from the eyes showed hemolytic *Staphylococcus aureus* and *Staphylococcus albus* on Dec. 10, 1945. Subculture from the mouth showed streptococcus and *Staphylococcus aureus*, the mixed growth of which was markedly hemolytic. On Dec. 18, 1945 smears from the mouth showed gram positive diplococci and gram

negative diplococci and many small gram negative bacilli. The smears were negative for Vincent's organisms. Broth culture from the mouth showed gram positive cocci in chains. Broth culture from the eyes showed gram positive cocci in chains and clusters. Blood culture was negative. The Widal and brucella agglutination tests were negative in dilutions 1:40 and 1:80. A roentgenogram of the chest on Dec. 10, 1945 showed a haziness in both upper lobes which appeared to be due to a peribronchial thickening. The right side showed the findings of early bronchopneumonia. There were enlarged glands in both hilar areas. Roentgen examination of the chest on



FIG. 1. Photograph of patient presented as case 2 on fifth day of hospitalization.

Dec. 24, 1945 showed a decided improvement in the appearance of the lung fields due to resolution of the bronchopneumonia. There were still several enlarged glands in the hilar areas.

Fever and increased pulse rate continued for 11 days after admission. On Dec. 9, 1945 there was considerable difficulty in swallowing. On Dec. 10, 1945 some of the bullae had entered the state of flattened skin lesions three-quarters inch to one inch in circumference. The lesions of the lips and eyes had become pustular. The

edema of the membrane of the mouth and palate was slightly less marked and liquids could be swallowed more easily. Skin and mouth lesions gradually improved. As the necrotic material in the mouth was removed the bright red ulcerations presented themselves. The skin of the feet became denuded. On Dec. 16, 1945 there was still considerable cervical gland enlargement. Areas of the mouth were denuded of membrane with areas of red tissue presenting. On Dec. 24, 1945 several finger nails and toe nails showed evidence of adjacent infection, and eventually all the nails sloughed off and new nails appeared.

Treatment consisted of boric acid solution, ophthalmic penicillin ointment to the eyes, a hydrogen peroxide mouth wash, supplemental vitamin therapy, penicillin 20,000 units intramuscularly every three hours from Dec. 8, 1945 to Dec. 16, 1945 and penicillin 15,000 units intramuscularly every three hours from Dec. 16, 1945 to Dec. 19, 1945. The patient was discharged on Dec. 24, 1945.

The following cases are listed:

Author	Year of Disease	Age	Sex	Duration	Complications	Remarks
Stevens and Johnson <sup>3</sup>	1922	8	M	About 3 months 6 weeks	Corneal scar	
Stevens and Johnson <sup>3</sup>	1922	7	M		Total loss vision	
Wheeler <sup>6</sup>	1927	8	M		Loss sight	
Bailey <sup>6</sup>	1927	39	M		Nails of all digits fell off; 3 years afterward blind due to corneal opacification	
Bailey <sup>6</sup>	1927	9	M	1 month	Poor vision; in institution of home for blind	
Bailey <sup>6</sup>	1927	7	M	18 days	Blind except for perception of light	
Rutherford <sup>7</sup>	1928		M	27 months	Removal both eyes	
Ginandes <sup>8</sup>	1931	5½	M	8 weeks		
Edgar and Syvertson <sup>9</sup>	1933	12	M	Temperature normal in 9 days; recurrence 6 mos. later—well in 6 days; recurrence 2 years later		Sodium salicylate used in treatment
Fletcher and Harris <sup>1</sup>	1932	16	M	3 weeks		
Fletcher and Harris <sup>1</sup>	1933	10	M	3 weeks		
Fletcher and Harris <sup>1</sup>	1933	10	M	1 week		
Fletcher and Harris <sup>1</sup>	1933	14	M	6 weeks		
Fletcher and Harris <sup>1</sup>	1934	4	M	4 weeks		
Fletcher and Harris <sup>1</sup>	1935	3	M	5 weeks		
Edgar and Syvertson <sup>9</sup>	1936	15	F	Discharged after 10 days		
Chick and Witzberger <sup>10</sup>	1936	11	M	Discharged 30th day. Severe oral Vincent's infection		Died few months later of carcinoma esophagus
Fletcher and Harris <sup>1</sup>	1937	6	F	5 days		
Fletcher and Harris <sup>1</sup>	1937	13	M	7 weeks		
Lever, W. F. <sup>11</sup>	1937	49	M	32 days		
Rosenberg and Rosenberg <sup>12</sup>	1937	11	M	3 weeks		Necropsy
Koke <sup>4</sup>	1938	9	M	3 weeks		
Fletcher and Harris <sup>1</sup>	1939	9	F	7 days		
Koke <sup>4</sup>	1939	39	M	5 days		
Koke <sup>4</sup>	1939	8	M	1 month		Symblepharon
Givner and Ageloff <sup>13</sup>	1939	23	M	1 month		
Givner and Ageloff <sup>13</sup>	1939	4	F	3 weeks		
Ageloff <sup>14</sup>	1940	4	F	20 days		
Fletcher and Harris <sup>1</sup>	1940	9	F	6 weeks		Neoprontosil used in treatment
Lever <sup>11</sup>	1941	35	M	2 months		
Fletcher and Harris <sup>1</sup>	1942	9	F	6 days	Conjunctival scarring and corneal opacity	
Murphy <sup>15</sup>	1943	22	M	4 weeks	Died Slough glans penis	
Fletcher and Harris <sup>1</sup>	1943	3	M	3 weeks		Sulfadiazine used in treatment
Fletcher and Harris <sup>1</sup>	1943	52	M	2 weeks		
Fletcher and Harris <sup>1</sup>	1943	7	F	3 weeks		
Fletcher and Harris <sup>1</sup>	1943	16	M	3 weeks		
Levy <sup>16</sup>	1943	7	M			Sulfonamide Sulfonamide Sulfadiazine
Kove <sup>17</sup>	1944	19	M	26 days		
Kove <sup>17</sup>	1944	19	M	86 days		
Erger <sup>18</sup>	1944	23	M	3 months	Bilateral corneal scarring	



## DISCUSSION

It may be of some significance in view of the unknown etiology that two cases of this rare syndrome have been admitted to one service within a period of one month occurring during the mild influenza epidemic of 1945. The disease may be an allergic reaction to bacteria without actual invasion of the microorganisms, or it may be of viral origin. The pathology is an intra- and intercellular edema of epithelium, with subsequent swelling of the squamous cells, widening of epithelial lymph spaces, formation of small vesicles and then their confluence with clinical vesiculation.<sup>19</sup> The lower layers of the cutis and subcutis are not involved.

This syndrome is more commonly found in Europe, Italy, the Balkan states, and Turkey, but seems to be on the increase in this country. Numerous degrees of eye involvement have been reported ranging from simple catarrhal conjunctivitis to ocular destruction. Whatever its designation it must be recognized as a condition in which the only serious end result is possible destruction of sight. The conjunctivitis is potentially destructive. It may have to be differentiated from foot and mouth disease, pemphigus vulgaris, varicella, vaccinia, and diphtheria.

## SUMMARY

Two more cases of the Stevens-Johnson syndrome may be added to the published cases. Bronchopneumonia with enlargement of the hilar glands occurred in both cases. The falling off of the nails of the digits which occurred in case 2 was mentioned in only one of the reviewed cases. Both cases were treated with penicillin; in comparison with the outcome of the published cases its effect upon the disease itself did not seem remarkable, although it no doubt was effective treatment for the pneumonia. The purulent conjunctivitis is the alarming symptom. The disease seems to be the expression of a systemic infection. The etiology is unknown.

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## COARCTATION OF THE AORTA \*

By JOSEPH R. FONTANETTA, M.D., *Brooklyn, N. Y.*

COARCTATION of the aorta is infrequently encountered clinically, although it is one of the most common congenital cardiac anomalies. In Abbott's series of 1000 cases of congenital cardiovascular defects, this condition was noted in 142 instances, being the primary lesion in seventy-nine. Baugh<sup>1</sup> places the incidence as high as one per thousand in the general population, while Blackford<sup>2</sup> maintains from his study of necropsy material that the frequency approximates one in 1550 cases. Similarly Levine<sup>3</sup> has stated that one in every 2000 persons in the general population has this abnormality. Abbott and Weiss<sup>4</sup> have emphasized the frequency with which this lesion is overlooked clinically. Undiagnosed cases are usually considered to be instances of essential hypertension, an error which stems principally from the fact that coarctation of the aorta is not generally kept in mind. Palpation for interscapular pulsation and measurements of the blood pressure in the upper and lower extremities would often establish the diagnosis in these cases. Occasionally in cases of coarctation hyperthyroidism has been erroneously diagnosed leading to unnecessary surgery.

A review of the literature indicates that the majority of reported cases of coarctation of the aorta were diagnosed either after cardiac symptoms had become manifest, or at necropsy. Emphasizing this point Blackford<sup>2</sup> in 1928 stated that of about 200 cases in adults already reported, only 19 were definitely recognized

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clinically. Lewis<sup>5</sup> similarly found that aortic coarctation is frequently not diagnosed during life and admitted that several cases under his observation went unrecognized for some time before diagnosis was established. Since the advent of World War II, however, it has been possible to diagnose coarctation of the aorta in many instances by means of the routine chest roentgenogram required of every examinee before entrance into the armed forces.

Abbott and Weiss<sup>4</sup> classify cases of coarctation of the aorta into the infantile and adult types. The first or infantile type, which is relatively rare, consists of narrowing of the isthmus of the aorta, more specifically that part between the left subclavian artery and the ductus arteriosus. It is usually associated with other important anomalies and is incompatible with long life, the infant usually dying before the ninth month. In the adult type of aortic coarctation there is a very localized constriction of the aorta at or most often just below the insertion of the ductus arteriosus. This type is much more common than the infantile type and less serious. Life expectancy generally ranges from the second to the fifth decade, although one patient has been reported to have lived to the age of 92 years. The causes of death in the adult type of coarctation of the aorta are usually cardiac failure, cerebral hemorrhage, dissecting aneurysm of the aorta and bacterial endocarditis. It is apparent that early recognition of aortic coarctation may prolong life by measures directed toward the prevention of these cardiovascular complications.

All grades of narrowing of the aorta occur, from that which is so slight that it can scarcely be seen on careful necropsy examination to complete local aortic obliteration. To compensate for the significant degrees of stenosis, there develops early in life a collateral circulation between the branches of the aorta, above and below the constriction. Some authors are of the opinion that the mechanical factor of stenosis is responsible for the elevation of the blood pressure in subjects with coarctation of the aorta. Rytland,<sup>6</sup> however, believes from his experimental evidence that the hypertension is actually due to renal ischemia resulting from the vascular constriction, being similar to the Goldblatt type of hypertension. Brotnner,<sup>7</sup> on the other hand, embraces the view that hypertension in aortic coarctation is due solely to the mechanical stricture of the aorta. He bases this hypothesis upon experiments in dogs in which he found that the hypertension was not due to a renal pressor substance.

At the Merchant Marine Medical Center in New York City we have seen two cases in which a presumptive diagnosis of coarctation of the aorta was made clinically, and confirmed by roentgenologic study.

*Case 1.* On December 9, 1944, a white merchant seaman, aged 19, had his initial physical examination before sailing. This young man's family and past history was negative. Previously he had been seen by several doctors who had found him physically fit. He gave no history of rheumatic fever, tuberculosis, syphilis, or nephritis. There were no complaints of dyspnea, cough, headache, syncope, vertigo, tinnitus, or pain in the legs.

Physical examination revealed a well built young man who showed no cyanosis of fingers or lips and no clubbing of the fingers. His examination was essentially negative except for his cardiovascular system. His heart rhythm was regular, and his pulse rate at the time of the examination was eighty-six. On percussion there was no left ventricular enlargement. No thrills were felt. On auscultation there was heard a slight systolic murmur at the apex and the base. Pulsations were felt

in the intercostal spaces over the left upper chest, but none was found in the interscapular region. There were no femoral pulsations. Blood pressure in the right brachial artery was 190 mm. Hg systolic and 100 mm. diastolic, in the left 192 mm. Hg systolic and 100 mm. diastolic. Blood pressure in the right femoral artery was 100

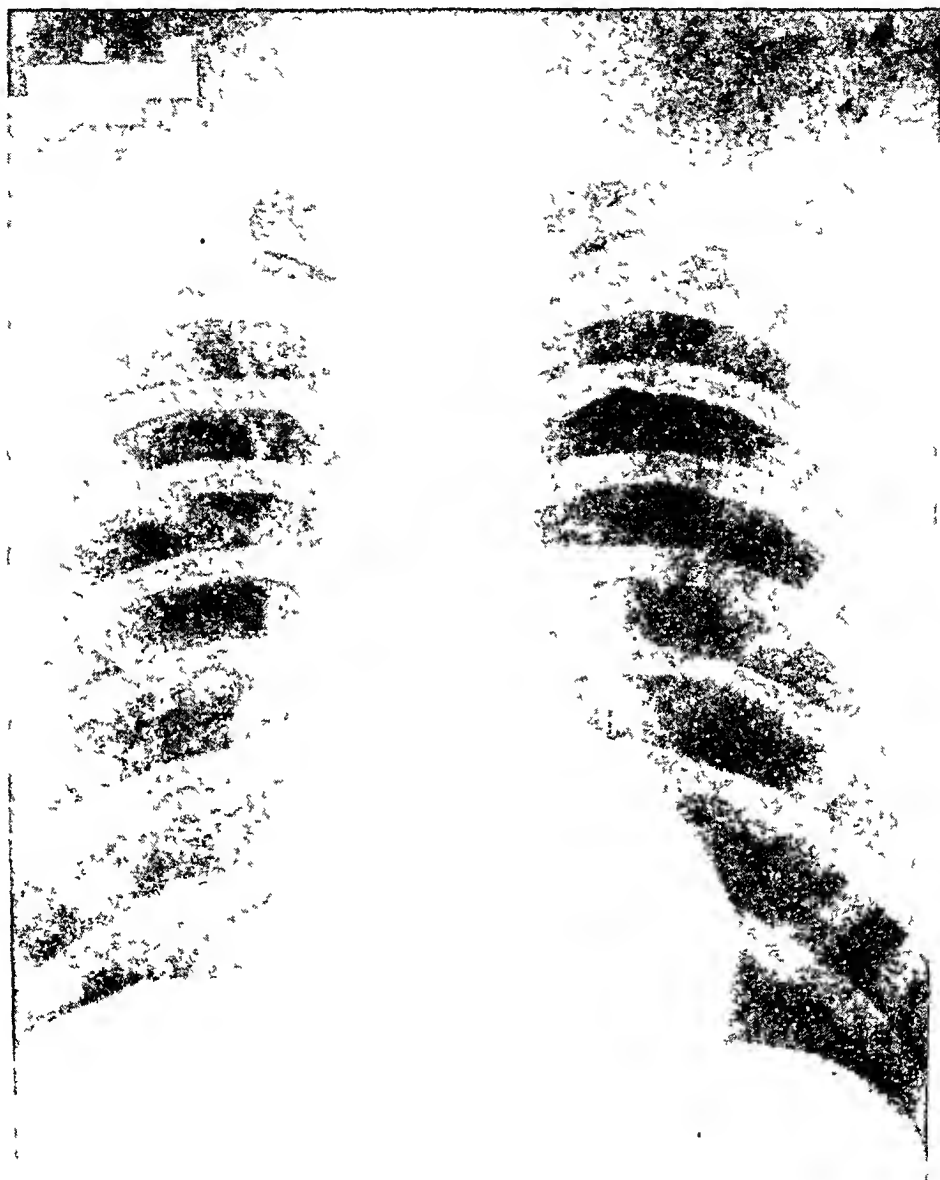


FIG. 1. Case 1. Scalloping of the lower rib margins on both sides, prominence of the left ventricle and a small aorta.

mm. Hg systolic and 60 mm. diastolic, and in the left 102 mm. Hg systolic and 64 mm. diastolic. Urinalysis was negative as well as the Kahn test. A presumptive diagnosis of coarctation of the aorta was made, and a chest roentgenogram was taken. The findings indicated scalloping of the lower rib margins on both sides, prominence of the left ventricle and a small aorta (figure 1).

*Case 2.* A 21 year old white merchant seaman before sailing had his initial physical examination at the Merchant Marine Medical Center. His history was essentially negative. Physical examination revealed a well built young man with negative physical findings except for his cardiovascular system. His only cardiac finding was a slight systolic murmur over the aorta, and hypertension. His blood pressure in the right brachial artery was 200 mm. Hg systolic and 120 mm. diastolic and in

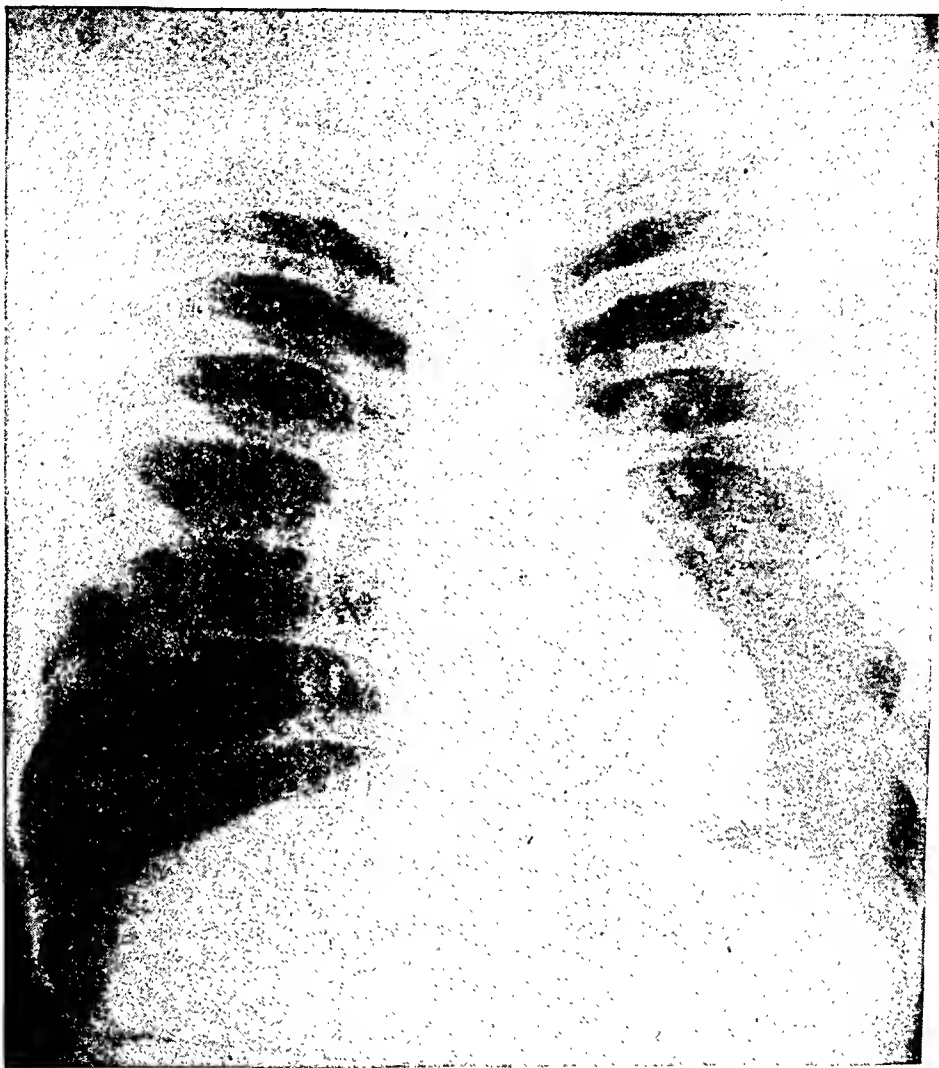


FIG. 2. *Case 2.* Scalloping of the ribs on both sides, a narrow aorta and slight prominence of the left ventricle.

the left 196 mm. Hg systolic and 114 mm. diastolic. Further investigation revealed a blood pressure of 120 mm. Hg systolic and 90 mm. diastolic in the right femoral artery and 114 mm. Hg systolic and 94 mm. diastolic in the left. No pulsations along the scapula were found. The femoral pulse could not be elicited. Urinalysis was negative. A presumptive diagnosis of coarctation of the aorta was made and a chest roentgenogram was taken. The findings showed scalloping of the ribs on both sides, a narrow aorta and slight prominence of the left ventricle (figure 2).

## SUMMARY AND CONCLUSIONS

1. Coarctation of the aorta is a common congenital vascular anomaly which is frequently unrecognized clinically.

2. The pathogenesis of elevated blood pressure in this condition has not been clearly established. Some authors believe that the mechanical effect of the stenosis of the aorta is the cause of the hypertension, whereas others try to connect it with the Goldblatt type of hyperpiesia.

3. A review of two cases of coarctation of the aorta is given with their case histories.

4. It is concluded that every case of hypertension in a young adult should be investigated with the possibility of coarctation of the aorta kept in mind.

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## ONCHOCERCIASIS: CASE REPORT \*

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ONCHOCERCIASIS is a tropical disease found only in sharply circumscribed areas of Central America and Africa. It is characterized by the occurrence of subcutaneous tumors or nodules due to the presence of the nematode *Onchocerca volvulus*. The disease is virtually confined to the colored race. Stitt<sup>1</sup> reports that in Africa infection in white men is rare, only some 20 cases having been reported. The case here presented occurred in a white male and the diagnosis was made while he was a patient in a hospital in England.

## CASE REPORT

A 32 year old, white, Free French sergeant was wounded in France in August, 1944 and was brought to England for treatment of his injured elbow. Physical examination revealed that in addition to a wound of the elbow he had a mass in the left rectus abdominis muscle below the umbilicus; this mass was considered to be a ventral hernia. The patient reported that this mass had been present for many years and that it had not undergone any change in size. On November 14, 1944 a spherical tumor, 1.5 cm. in diameter, was removed from the posterior sheath of the left rectus abdominis muscle. Except for a soft yellowish area at one pole it appeared on section as a typical dense white fibroma.

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FIG. 1. Photomicrograph of fibroma with sections of *Onchocerca volvulus* cut transversely and longitudinally.  $\times 50$ .



FIG. 2. Photomicrograph showing microfilariae within the adult *Onchocerca volvulus*  $\times 300$ .

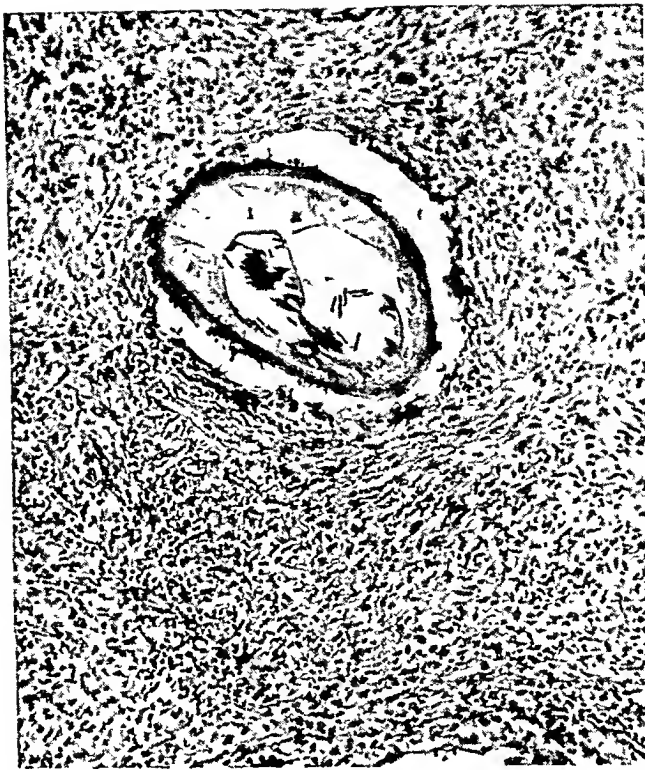


FIG. 3. Photomicrograph of transverse section of *Onchocerca volvulus* with surrounding inflammatory reaction.  $\times 100$ .

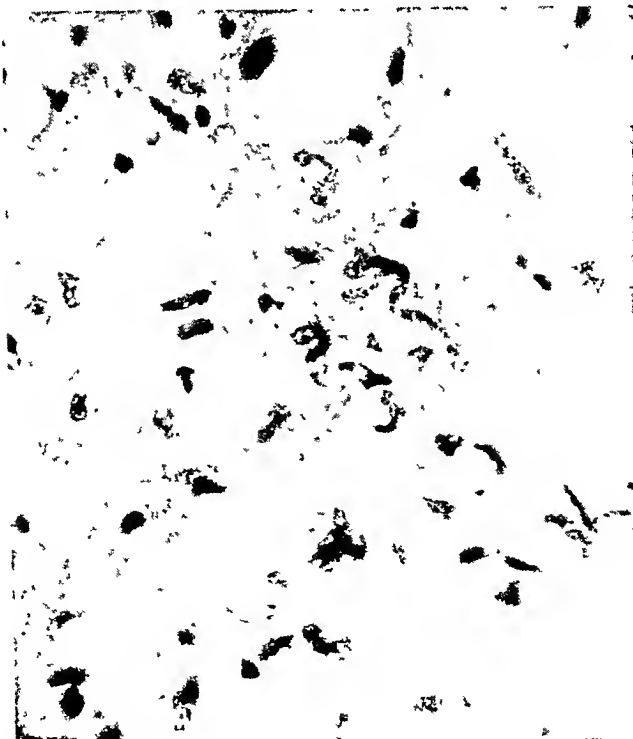


FIG. 4. Photomicrograph showing microfilariae free in the tissue of the nodule.  $\times 300$ .



Microscopic examination of the histological preparation of this fibrous tumor revealed the adult filarial worm, *Onchocerca volvulus*, surrounded by dense fibrous connective tissue (figure 1). Contained in it were myriads of microfilariae (figure 2). In some areas the microfilariae were free in the fibrous tissue. Around some of the portions of the adult worm there was marked inflammatory reaction with infiltration of the tissues by polymorphonuclears, round cells, and eosinophiles. In some areas of the section the eosinophile infiltration was quite marked.

The blood smear on November 18, 1944 showed 17 per cent eosinophiles. There were no other nodules present and there was no history of past or recent eye disease. Ophthalmological examination was negative. This soldier's tropical service was significant as it took him during the period 1931 to 1944 into Gambia, Congo, and Cameroon; these are areas where onchocerciasis is endemic.

### DISCUSSION

The clinical significance of African onchocerciasis is usually not great except that it is a cause of unexplained eosinophilia. The microfilariae migrate in the subcutaneous tissues of the host for varying distances but, except for the patient who is specially sensitive to the parasite or its toxins, they do little harm. In the Central American type, in which the lesions tend to be located on the head, the microfilariae are prone to invade the eyes and cause iridocyclitis, keratitis, pannus formation, and eventual blindness. In the African type, in which the lesions tend to be located on the trunk, involvement of the eyes is exceptional.

The disease is transmitted by flies of the genus *Simulium*. One may reasonably speculate that this is an old disease in which parasitism has been successful to the point where infection results more in inconvenience than in disease. Treatment consists in removal of the nodule. Following this the microfilariae in the tissues survive for a while but they eventually die.

### SUMMARY

A case of onchocerciasis is reported which occurred in a young adult white male of French nationality and which was diagnosed while he was a patient in a hospital in England.

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## ANAPHYLAXIS TO THE INJECTION OF NICOTINIC ACID (NIACIN); SUCCESSFUL TREATMENT WITH EPINEPHRINE \*

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AN anaphylactic reaction to nicotinic acid has not been previously reported in the literature, although sensitivity to the drug has been noted before. The present widespread use of nicotinic acid, both as a vitamin and as a drug, makes

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reports of these accidents mandatory, because they will undoubtedly be experienced by others. The morbidity can probably be avoided by a careful questioning of the patient before the injection of nicotinic acid is given. In our cases, the usual treatment for anaphylactic shock was sufficient to overcome the symptoms in these patients.

Rachmilewitz and Glueck<sup>1</sup> described the occurrence of an urticarial dermatitis with flushing of the face and severe itching in a patient with pellagra after he had taken two 50 mg. doses of nicotinic acid orally. Chen, Rose and Robbins<sup>2</sup> found no irritant effect from a 1 per cent solution of nicotinic acid injected intradermally. In spite of this, Watrous<sup>3</sup> reported four cases of severe itching and diffuse erythema of the skin in industrial workers exposed to nicotinic acid. Other workers handling nicotinic acid under the same circumstances showed no reaction. Powdered nicotinic acid rubbed into a patch of skin of some of the workers caused itching and erythema, but this result was not evident in others. There was no correlation between smoking and the susceptibility to dermatitis. It must certainly be that some of the workers were allergic to nicotinic acid and some were not.

Nicotinic acid (niacin), one of the B vitamins, has come into widespread use as a drug, because of its vasodilating properties. Especially is this true in the treatment of Menière's syndrome and certain cases of migraine headache. In some cases of these conditions it has had an extremely salutary effect. Intravenous injections of an appreciable amount of nicotinic acid causes in nearly all individuals a bitter taste on the tip of the tongue in about 17 to 18 seconds. This may be considered to be the arm to tongue circulation time of the nicotinic acid. In about one minute a widespread flush appears all over the body. This may last for two or three hours. This flush is desirable and is the basis for the use of nicotinic acid as a drug. The flush of the skin is considered presumptive evidence that the blood flow is increased in the internal structures as well. In the case of the ingestion of tablets of nicotinic acid, the flush may appear irregularly in different individuals and comes on after several hundred milligrams of nicotinic acid are taken. Nicotinic acid amide does not give a flush, no matter how much is taken.

The flush described above is the usual reaction to nicotinic acid given intravenously, and besides being somewhat disagreeable, entails no further difficulty. If after the first or after a subsequent injection of nicotinic acid, the patient develops dizziness, a soft, rapid, thready pulse, a spasmodic cough, a sensation of choking and collapse, it is safe to assume that an anaphylactic shock has occurred. In the two cases about to be described, both patients experienced allergic reactions to an oral dose before receiving the intravenous dose which precipitated the anaphylactic shock.

#### CASE REPORTS

*Case 1.* R. C., a 34 year old pregnant woman, was sent for study by her obstetrician because of an extremely reddened and sore tongue. This condition was present in spite of the use of nicotinic acid amide, 150 mg. daily, and riboflavin, 15 mg. daily. Because of the possibility of poor absorption from the intestinal tract 25 mg. of nicotinic acid were given intravenously. The product used contained 50 mg. of nicotinic acid per c.c. as the monoethanolamine salt. Within two minutes, the patient became dizzy, developed extreme shortness of breath and a short spasmodic cough.

The pulse was 110 per minute, thready and somewhat irregular. The blood pressure registered 90 mm. Hg systolic and 60 mm. diastolic, the respirations were 36 per minute and the rectal temperature was 98° F. The patient was gasping for breath and was in collapse. Five minims of epinephrine 1/1000 solution was given intramuscularly. There was some relief of the oppressive symptoms, but these recurred in about 20 minutes, and required the same dose of epinephrine to be given again. The patient had been placed on the examining table and was kept warm. Although she reacted well, she was hospitalized for the night. She required no further treatment. The next day the patient was skin tested with 0.05 c.c. of a 1:20 dilution of the material that was used for the intravenous injection. A fairly large wheal with a surrounding erythema occurred in five minutes.

Careful questioning of the patient revealed that each time a nicotinic acid amide tablet had been taken by mouth, her lower lip had become swollen. This was not known to me at the time of administering the injection. This patient had never had any previous allergic symptoms of a definite nature, although she did have a history of migraine headaches which might conceivably have had an allergic background. It should be noted that this patient had only one injection of nicotinic acid. The sensitization came about apparently through previous medication with nicotinic acid amide by mouth.

*Case 2.* R. K., female, aged 25 years, complained of severe unremitting left-sided headaches that lasted over a period of 10 days. The headaches were not accompanied by nausea or vomiting. This patient also suffered from ragweed hay fever. No organic disease could be found to account for the severe headaches. She presented some personality problems such as overprotection by her relatives and a feeling of guilt and insecurity over an impending trip planned in order to break away from her family. Medications of various sorts had had no effect on the headache. Injection of 1 c.c. of procaine into some tender spots in the muscles of the right occipital region relieved the headache immediately, but the pain returned within an hour.

It was decided to try nicotinic acid by mouth, 50 mg. three times a day and intravenously as well, in advancing doses. Intravenous therapy with the same preparation used in the first case was started with a dose of 5 milligrams. There was no flush reported by the patient. In all patients previously given this medication a flush was obtained with this dose intravenously. At the time, this fact did not occasion any suspicion of an altered reactivity to the drug. The patient was given 10 mg. the next day, and 15 mg. on the succeeding day. The headaches were not relieved. The patient presented no untoward response, except that the flush was not obtained. It is uncertain what meaning could be attributed to this lack of an expected response. On the fourth day, 20 mg. of the drug were given. Within several minutes, the patient became dizzy, started to cough and choke and went into shock. The blood pressure reading was 80 mm. Hg systolic and 70 mm. diastolic, the pulse rate was 100 and the pulse was thready. The rectal temperature was 98° F. An intramuscular injection of 6 minims of epinephrine was given immediately. This required repetition in 15 minutes because of the return of the spasmodic cough and the sensation of choking. The patient was taken home after two hours. She required a third injection of epinephrine about six hours after the first injection. When she was visited the following day she was entirely well.

Careful questioning of the patient after the reaction had occurred revealed the pertinent fact that the patient developed dizziness and a slow hacking cough about 10 minutes after the third injection and also about 10 minutes after taking a 50 mg. tablet of nicotinic acid on the night before the reaction. Had this important fact been known earlier, the subsequent injection would not have been given. This patient refused to have a skin test done with nicotinic acid, so that data on this point are unavailable.

## COMMENT

As stated above, anaphylaxis to nicotinic acid has not been previously described, although some cases of sensitivity have been recorded.<sup>1, 3</sup> The fact that nicotinic acid is not a protein is no bar to its acting as an antigen. The simplest explanation of this phenomenon is that the drug acts as a "hapten" which combines with the protein of the host after absorption into the body. This hapten-protein combination forms a new allergen specific for itself and not for the protein of the individual. Once a person or animal is sensitized to the hapten-protein combination, the hapten, e.g. nicotinic acid, alone can cause the allergic reactions. This explains the rapidity with which symptoms occur.<sup>4</sup>

There are several case reports of anaphylaxis, even death, due to thiamin.<sup>5</sup> In one recorded case, symptoms appeared after the first injection of thiamin, which raised the question whether the allergy was inherited or perhaps acquired from thiamin intake in the food or the vitamin by mouth. In the first case that is described in this paper, the patient was apparently sensitized by taking nicotinic acid amide by mouth. She had never taken nicotinic acid before.

Nothing that is stated here should be construed as an attempt to hamper the legitimate use of a worthwhile drug. It is merely desirable to point out that anaphylactic reactions may occur with nicotinic acid, and that the usual methods of treatment of anaphylactic shock are useful in coping with this condition. In both our cases, epinephrine in the usual dosage was effective in overcoming the anaphylactic shock. However, this must be given immediately, because by analogy with some of the cases of thiamin allergy, death might otherwise eventuate.

An even more important factor is the possibility of prevention of the reaction. If a patient has been on nicotinic acid or nicotinic acid amide therapy and an injection of nicotinic acid is projected, the patient should be quizzed as to possible sensitivity before the injection is given. If several injections are given, questions as to sensitivity should precede each injection. This warning applies even more definitely to patients who are allergic to other substances. In both of our cases the morbidity could have been avoided if the possibility of allergy to nicotinic acid had been entertained and appropriate questions asked. An intracutaneous test with 0.05 c.c. of a 1:20 dilution of the material to be injected may, if a positive test is obtained, indicate sensitivity. Further work on this point appears to be indicated.

## SUMMARY

1. Two cases of anaphylactic shock caused by sensitivity to nicotinic acid (niacin) are described.
2. The usual treatment with epinephrine intramuscularly was effective in relieving the symptoms in both cases.

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## A CASE OF FULMINATING MENINGOCOCCEMIA EXHIBITING THE WATERHOUSE-FRIDERICHSEN SYNDROME AND DEMONSTRATING THE VALUE OF CORTICAL EXTRACT ADMINISTRATION \*

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PRATT-THOMAS in 1945<sup>6</sup> reviewed 184 cases of fulminating meningococemia with eight recoveries. Prior to 1940, all cases were uniformly fatal.

This is a case of Waterhouse-Friderichsen syndrome in a 17 year old white female who fulfilled practically all the clinical criteria and, in addition, yielded meningococci on blood culture. She developed gangrene of three extremities and bilateral ulnar nerve paralysis but recovered. The case presents several unusual features.

### CASE REPORT

The patient was a 17 year old white female waitress who entered Meadowbrook Hospital on Oct. 12, 1945, with a chief complaint of chills and fever of several hours' duration. On the day preceding her admission, Oct. 11, 1945, at about 3:30 p.m. she complained of a chill which was followed by fever of 102° F. She went to bed feeling she was coming down with the grippe. She continued to have intermittent chills with fever ranging between 102° and 103° F. throughout the night. At 3 a.m. the following morning, when she got up to go to the bathroom, she complained of pains in her legs and difficulty in walking. At 7 a.m. she noticed purple areas on her legs and red pin-point areas on her arms. A local doctor was called who advised immediate hospitalization and she was brought to the hospital by ambulance at 8:45 a.m. Oct. 12, 1945.

Her previous medical history revealed a possible rheumatic diathesis. As a child she had complained of frequent growing pains and epistaxis. There was, in addition, a familial history of rheumatic fever.

On admission physical examination revealed a fairly well nourished white adult girl who appeared acutely ill. Her lips and skin appeared cyanotic, her skin having a dusky color. Her face was puffy. There were petechiae and large and small purpuric areas over the face and body. These, however, were much more marked over the extremities and particularly the lower extremities. The purpuric areas could be

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From Meadowbrook Hospital.

seen to increase in size during the process of examination. Petechial spots were seen also in the mouth, on the hard palate and on the conjunctivae with sub-conjunctival hemorrhage. She was bleeding from the lower lip and gingivodental margins. Her extremities were cool to the touch. The temperature was 102.6° F. The blood pressure was 80 mm. Hg systolic and 66 mm. diastolic and the ventricular rate was 150 and regular. Respirations were 48. The patient appeared very apprehensive and kept biting her lower lip. Although not comatose she was delirious and remained so for several days. Her neck was supple but she had a positive Brudzinski sign. Her deep reflexes appeared to be hypoactive. However, these were difficult to evaluate owing to the presence of muscle spasm. Her thighs and calves were full, tense, and tender. They felt as if there was exudation or extravasation present involving the

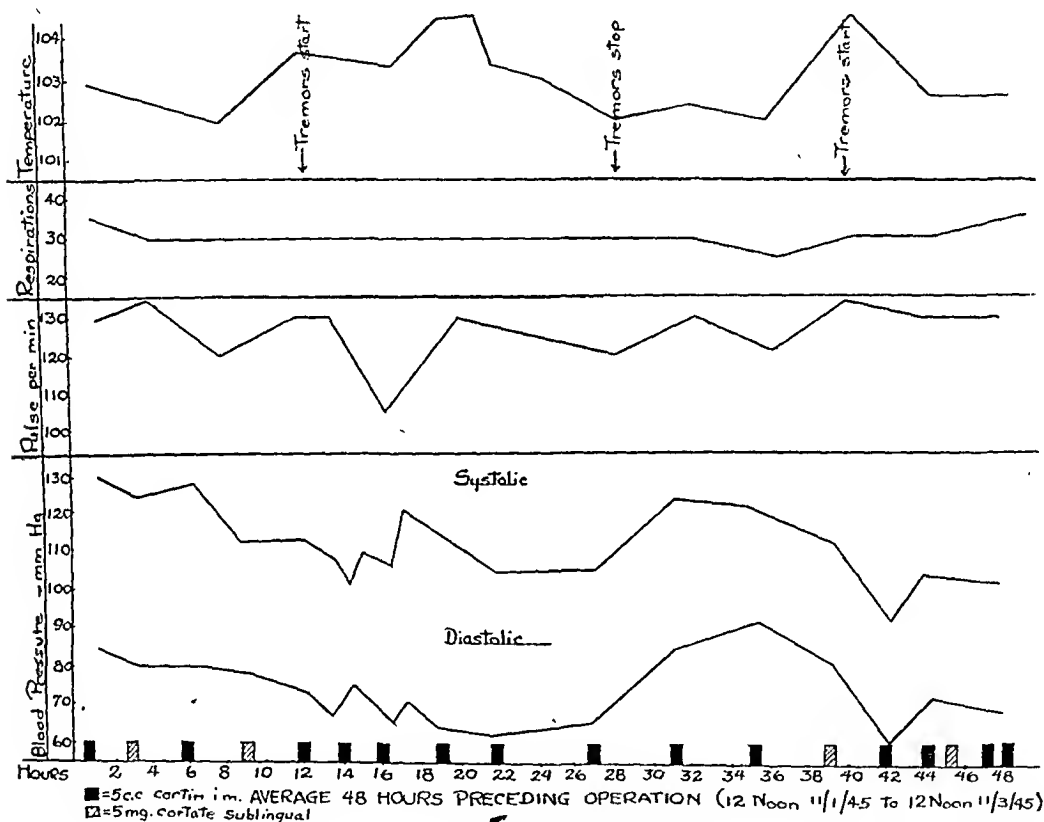


FIG. 1.

muscle and subcutaneous tissues. There was generalized muscle tenderness. The remainder of the physical examination was non-contributory. A spinal tap done at the time of admission showed crystal clear fluid at 8 mm. of mercury with 350 red blood cells per cubic millimeter, no white blood cells; sugar, 80 mg. per cent; protein, 53 mg. per cent. The blood count showed 24,000 leukocytes with 90 per cent polymorphonuclears. A provisional diagnosis of meningococcemia with Waterhouse-Friderichsen syndrome was made. The patient was placed in shock position and blood was drawn for chemistry and culture before beginning intravenous therapy. She was given immediately 500 c.c. of 5 per cent glucose and saline containing 50,000 units of penicillin. She received intravenously, 10 c.c. of cortin\* and 5 grams of sodium sulfadiazine. Continuous infusions were maintained during the next 10 days.

\* Cortin, Upjohn. (Adrenal cortical extract, 50 dog units per c.c.)

During this time she received 3,000 c.c. of whole blood, 2,850 c.c. of plasma, 12,300 c.c. of saline, 3,300 c.c. of 5 per cent glucose and saline, and 4,200 c.c. of  $\frac{1}{6}$  molar lactate as well as 2,075,000 units of penicillin (roughly 50,000 units of penicillin for every 500 c.c. of fluid) and two grams of sodium sulfadiazine every four hours intravenously (into the tubing). Vitamins also were added to the infusion and given by mouth as well. Cortin was administered during this period intravenously, 5 c.c. every three hours. An attempt was made to maintain a schedule giving 400 c.c. of  $\frac{1}{6}$  molar lactate a day with 500 c.c. of blood and 500 c.c. of plasma, supplemented with glucose and saline.

*Laboratory Examinations.* Blood on admission showed non-protein nitrogen 41 mg. per cent; blood sugar, 170 mg. per cent;  $\text{CO}_2$  combining power, 41 vol. per cent (drawn on Oct. 17, 1945). Twelve days later non-protein nitrogen was 20 mg. per cent; creatinine, 1.5 mg. per cent; sugar, 94 mg. per cent; chlorides, 462 mg. per cent. The blood culture drawn on the day of admission was reported as positive for meningococci and was negative when repeated on the third hospital day. All succeeding cultures were sterile. Total protein on October 17 was 4.9 gm. per cent with albumin 2.9 gm. per cent and globulin 2.0 gm. per cent. Repeated on October 23, total protein was 4.5, albumin 3.0, globulin 1.5 gm. per cent.

Blood Count:	Oct. 12 (on admission)	Oct. 16	Oct. 22
Hemoglobin		90.4	95
Red blood cells	3,000,000		
White blood cells	24,000	18,000	14,100
Polymorphonuclears	90%	78	74
Lymphocytes	10%	22	22
Monocytes			4

Coagulation time on admission was four and one-half minutes and bleeding time three minutes.

Urinalysis showed many red blood cells on the day following her admission to the hospital. This persisted up to Nov. 9, 1945, in decreasing numbers. The urine showed a faint trace of albumin on admission and continued to do so intermittently since.

*Course.* The purpuric areas enlarged and became confluent during her first hospital day, eventually covering practically all of the lower portions of her legs and feet. By 8 p.m. on the day of admission her right foot had become quite cold from the ankle down. It was not possible to palpate the dorsalis pedis pulsation on either foot although popliteal pulsations were palpable bilaterally. On the morning of her second day, Oct. 13, 1945, both feet were cold as was also the distal half of the left lower leg. Both feet appeared black, the left more so than the right. Both popliteal pulsations were still palpable. The lower legs and feet seemed greatly swollen and tense. She complained of pain in both lower extremities. The right foot improved somewhat during the day so that in the evening of Oct. 13, 1945, it began to feel warmer. On Oct. 14, 1945, the right foot was quite warm and appeared less dark. The left leg was warm to the ankle. Large subcutaneous blebs began to appear on both lower extremities. On Oct 15, 1945, both feet were warmer and improved in color. The skin of both lower legs and feet, however, continued to form blebs which broke down leaving many raw ulcerated areas. By Oct 30, 1945, there was a proliferation of granulation tissue on the right leg and foot and to lesser extent on the left. The skin of the feet, however, was still in the process of sloughing. Azochloramid soaks were applied to the legs in an attempt to increase the sloughing process and possibly to reduce the growth of redundant granulation tissue. The ulcerating process continued,

so that several days later both legs were devoid of epithelium from the mid-calves to the ankle. Granulation tissue grew in abundance on both legs, more so on the right. The skin of both feet appeared black and gangrenous but did not slough. At this time, her second hospital week, it was noticed that the patient held her hands in the main-en-griffe position. Her legs gradually became grossly infected. She began to have chills and fever ranging to 104° and 105° F. and Nov. 4, 1945, tendons and muscle bellies were exposed. These appeared dark and infected. On Nov. 4, 1945, both legs were packed in ice below the knee and on the following day bilateral amputations, 2 inches below the knees, were performed under nitrous oxide anesthesia. No attempt was made at that time to prepare skin flaps or to close the wounds which were infected. Postoperatively, the stumps were treated with azochloramid soaks and daily irrigations. Skin traction was applied bilaterally.

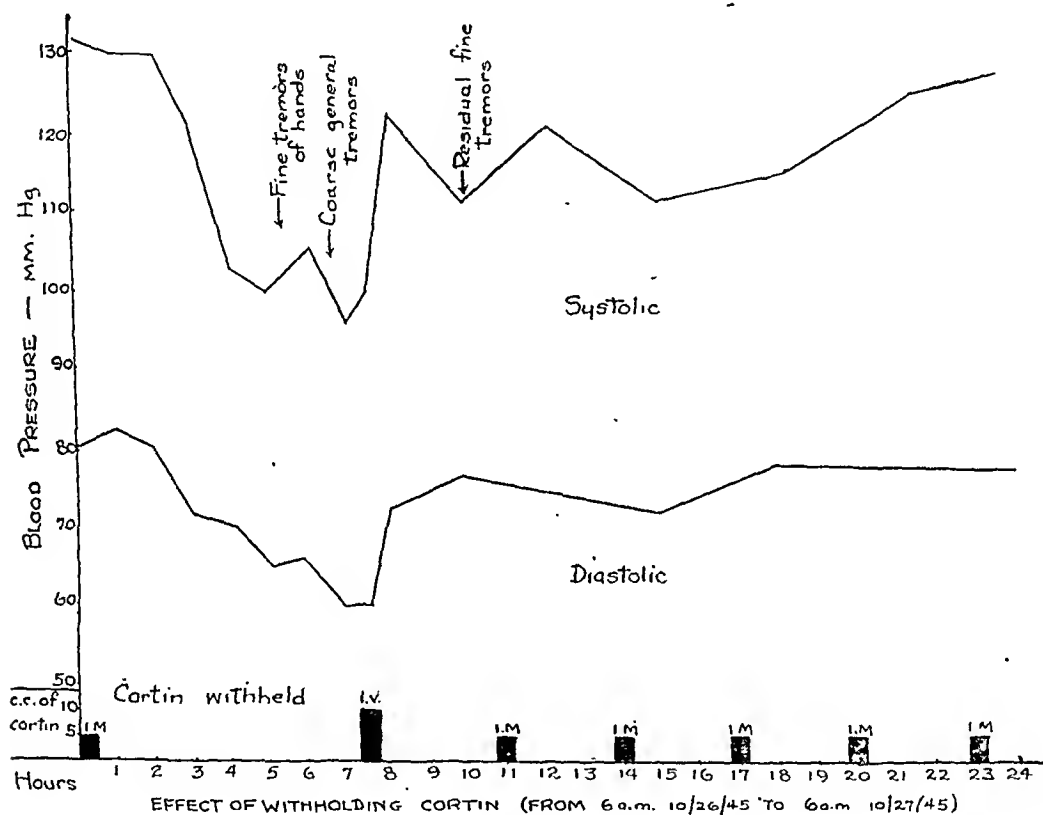


FIG. 2.

The distal phalanx of the index finger of right hand and the terminal phalanx of the right middle finger appeared cold and black on the second day of her admission. By the third day, they were definitely gangrenous and dry. The purpuric areas on her trunk and upper extremities had ulcerated, the smaller ones having healed and the larger ones healing. The blood pressure on admission was 80 mm. Hg systolic and 60 mm. diastolic and remained fairly constant even with rather large doses of cortin until the following day when it rose to 100 mm. systolic and 74 mm. diastolic, increasing gradually to 130 mm. systolic and 80 mm. diastolic on her fourth hospital day. At this point an attempt was made to reduce the cortin from 5 c.c. intramuscularly every three hours to 5 c.c. every six hours with no apparent ill effects. The following day an attempt was made to reduce the cortin to 5 c.c. every 12 hours; however, after seven hours without cortin, the pressure had fallen from 130 mm. systolic and 80 mm.



diastolic to 116 mm. systolic and 65 mm. diastolic and the patient developed generalized somatic tremors. The dose of cortin was again restored to 5 c.c. every 3 hours with an immediate dose of 10 c.c. intravenously, and in one hour the tremors had ceased. The blood pressure, however, continued to fall during the next four hours reaching 104 mm. Hg systolic and 68 mm. diastolic, then it rose again so that by the following morning it was 130 mm. systolic and 80 mm. diastolic. On Oct. 18, 1945, cortin was purposely withheld. After seven hours fine tremors appeared beginning in her hands, spreading to the face, becoming generalized and coarser and being maximal eight and one-half hours following the last dose. During this period, the blood pressure dropped from 130 mm. Hg systolic and 80 mm. diastolic to 110 mm. systolic and 45 mm. diastolic. At this point 10 c.c. of cortin were administered intravenously. Again the tremors disappeared, and the blood pressure began to rise so that it was 112 mm. systolic and 64 mm. diastolic in one hour; seven and one-half hours later it had risen to 130 mm. systolic and 75 mm. diastolic. The diastolic pressure did not reach 80 mm. until the following morning. The pulse rate rose from 108 to 140 with maximal drop in blood pressure and returned to original rate as blood pressure rose. On Oct. 26, 1945 cortin was again withheld. Seven hours from the last dose, the blood pressure had dropped from 132 mm. systolic and 80 mm. diastolic to 96 mm. systolic and 60 mm. diastolic, and the patient exhibited generalized coarse tremors. At this time she complained of a drowsy sensation and a feeling of weakness. Cortin was resumed at this point (10 c.c. intravenously) with the gradual disappearance of the tremors in three hours. The blood pressure rose to 122 mm. systolic and 72 mm. diastolic within the hour and had returned to the original pressure by the following morning. The pulse rate rose and fell inversely to the blood pressure. On each occasion the patient received 5 c.c. of cortin intramuscularly every three hours following the initial dose of 10 c.c. intravenously. A blood chloride level was taken before the cortin was discontinued and was reported as 510 mg. per cent and again before cortin was resumed and was reported as 577 mg. per cent. On Oct. 27, intramuscular cortin 5 c.c. was reduced from every three hours to every six hours and 10 mg. of cortate\* were given sublingually every six hours alternately so that the patient received some form of cortical therapy every three hours. This was continued to the time of operation. However, it was noted that the blood pressure tended to be lower with this form of therapy and on several occasions tremors developed; the latter usually occurred when the blood pressure dropped below 100 mm. Hg systolic. Occasional supplemental doses of cortin had to be given to stop the tremors and elevate the pressure. During one of the episodes of generalized tremors and hypotension, a blood sugar determination read 120 mg. per cent. It was further noted that the drops in blood pressure seemed to coincide frequently with sharp elevations in temperature. The night preceding her operation she was given cortin 5 c.c. and sodium chloride 4 gm. per os every three hours with 10 c.c. of cortin intravenously immediately preceding the operation. Cortin was given, 5 c.c. intramuscularly, every three hours following operation as well as saline, plasma, and whole blood. A continuous intravenous drop was maintained for the first four post-operative days during which time she received 7,000 c.c. of 5 per cent glucose and saline, 2,000 c.c. of saline, 2,000 c.c. of plasma and 1,000 c.c. of whole blood. Penicillin was given at the rate of 50,000 units for every 500 c.c. of intravenous fluid along with 20,000 units every three hours intramuscularly. One ampule of synkamine was given daily. On the first post-operative day cortin and cortate were administered alternately every three hours, and the temperature went to 106° F. but dropped rapidly to 102°. On this day her blood pressure tended to be rather low, and tremors were noted almost all day. This is the last time the patient exhibited tremors, and since then her blood pressure has been well maintained. Cortin was decreased gradually and on Nov. 9, the fourth post-operative day, it was discontinued

\* Cortate, Schering. (Desoxycorticosterone acetate, 5 mg. per c.c.)

with no apparent ill effects. On Nov. 7 physiotherapy was started in an attempt to improve the function of her hands. Hypesthesia, anesthesia, and paralysis were present in those portions mediated by the ulnar nerves. During the first 10 days of her illness, she ran a fever ranging between 103° F. and 104° F. However, after the infusion was cut on the tenth day, it ranged between 100° and 102° F. and gradually climbed to 104° and 105° F. several days preceding amputation of her legs. Latterly the temperature curve was of a septic type. Following the amputation the temperature gradually dropped and became normal on Nov. 15, 1945. The radial pulse which had been imperceptible on admission could be palpated that same evening and was fairly strong by the second day. Penicillin was discontinued on Nov. 13, 1945, the patient having received a total of 6,060,000 units. She received in addition during her hospital stay, 99 gm. of sulfadiazine, the last 30 gm. being given intermittently after the first 10 hospital days.

Blood Counts:	Oct. 31	Nov. 14	
Hemoglobin	95	50%	
Red blood cells		3,500,000	
White blood cells	8,200	4,000	
Neutrophils	60	60	
Lymphocytes	40	40	
Chemistry:	Nov. 2	Nov. 8	Nov. 14
Non-protein nitrogen		21	23
Creatinine		1.5	1.5
Sugar	120	95	85
Chlorides			445
Total protein	4.2	4.6	
Albumin	3.2	2.9	
Globulin	1.0	1.7	

Report of Pathologist: \* Nov. 5, 1945. *Specimen:* Both legs.

"Specimen consists of two legs which have been amputated just below the knee. The skin of both feet extending from the toes to the region of the ankle joint shows black gangrenous discoloration. From each ankle to the sites of amputation there are large irregular deep ulcers many of which are confluent and replace the greater portion of the skin surface. There are extensive areas of granulation tissue centrally situated in many of the ulcers and superimposed upon these there are broad islands of re-epithelialization. The muscles and tendons of the anterior aspect of the right ankle are exposed. The involved skin appears to extend up to the very line of surgical transection. Section through the major vessels just distal to the line of transection shows no evidence of grossly visible thrombosis or inflammation of the major veins or arteries at these sites. However, in the right leg just below this area the posterior tibial vein contains an elongated well formed but non-adherent thrombus which is dark red and presents gray surface striations. The other large vessels more distal to these areas do not appear to be involved. On section into the ulcerated areas of the skin and subcutaneous tissue the underlying connective tissues appear indurated and edematous. Beneath each ulcerated zone the veins appear to be distended and occluded by soft grayish-brown and dark red blood clots, some of which are loosely adherent while others are easily dislodged. The arteries, however, are not affected. A few areas in the right leg present bright, opaque yellow, irregular zones up to 3 cm. in diameter resembling infarcts of the subcutaneous fat with thin bright red hemor-

\* Dr. Theodore J. Culphey, Chief of Department of Pathology.

rhagic borders. The muscle and deep fatty tissues are softened and show reddish-brown discoloration. On section into the under surface of both feet the gangrene appears to involve the entire skin layer while the underlying muscle and fat show reddish-brown discoloration. The bones and joints do not appear to be involved.

*"Microscopic:* Sections show extensive chronic productive inflammation of the skin and subcutaneous tissues with interstitial hemorrhage and extensive infiltration of polynuclear cells. Many of the areas of skin and subcutaneous tissue appear gangrenous and stain poorly, while the major arteries and veins show no evidence of thrombosis. Many of the central vessels, especially the veins, appear to be occluded and distended by blood clots with evidence of organizing change at the periphery. In

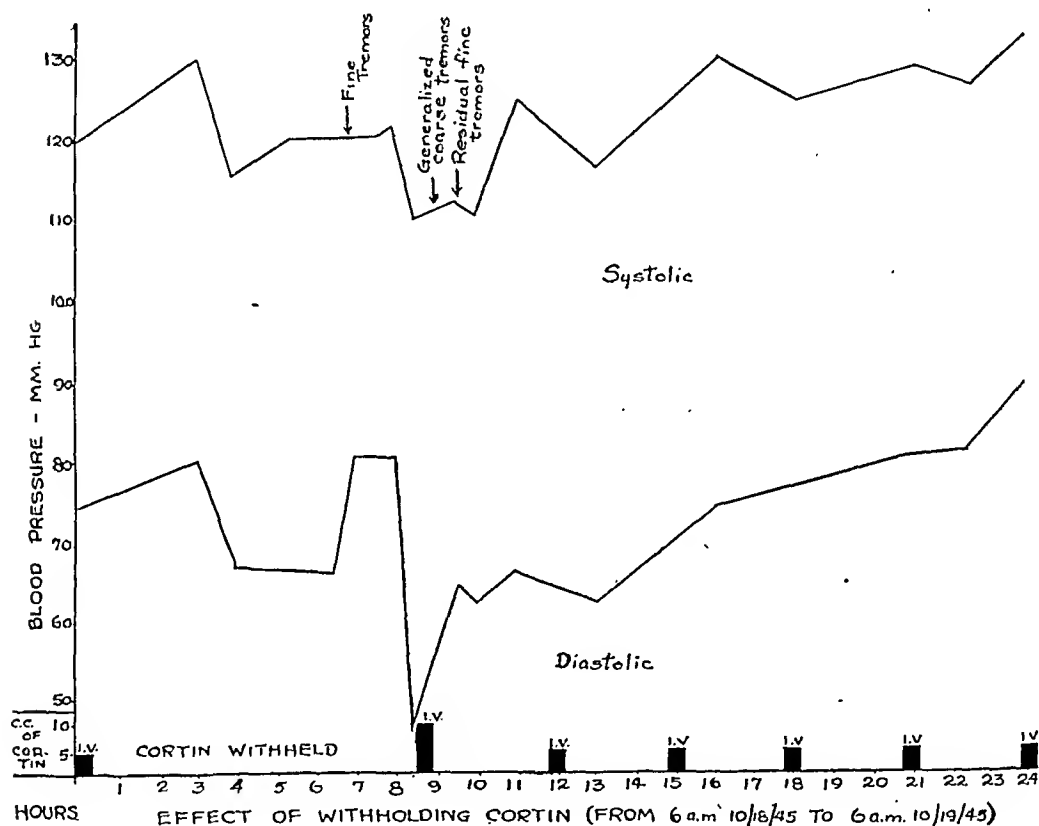


FIG. 3.

some sections the small arteries are also occluded and show evidence of similar organization of the blood clots. A prominent feature is the muscular hypertrophy of many of the arterioles which, however, show no evidence of blood clot.

*"Diagnosis:* Gangrene of skin secondary to organizing septic arterial thrombosis with coincident arteriolar medial hypertrophy."

### DISCUSSION

Ectodermal necrosis and slough have been reported<sup>2, 7</sup> and also gangrene involving several toes requiring amputation.<sup>4</sup> The case presented here exhibited numerous areas of ectodermal slough involving the trunk and all extremities, gangrene of the skin of the feet and both lower legs and the distal half of the right index finger and terminal phalanx of the right middle finger. The pathological

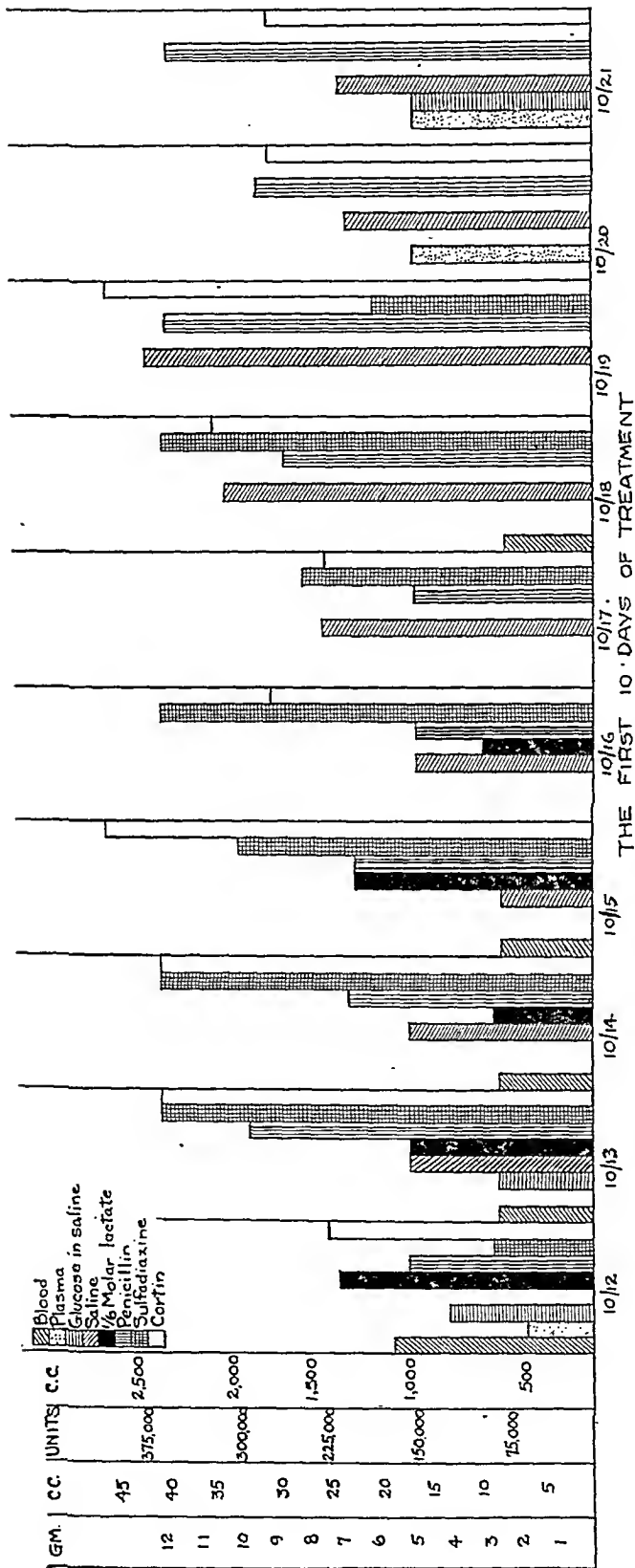


Fig. 4.

report noted the presence of septic arterial thrombi and arteriolar medial hypertrophy. The latter would be of therapeutic interest if the hypertrophy could be interpreted as arteriolar spasm which conceivably could add to the extent and severity of tissue necrosis. Such an assumption could not be made from a microscopic examination alone.

The patient further presented involvement of both ulnar nerves. This became apparent about the end of the first week and manifested itself by the main-en-griffe position of both hands with hypesthesia, anesthesia and paralysis of those portions mediated by the ulnar nerves. At this writing, two months after onset, she gives no evidence of return of function although there is some lessening of the degree of anesthesia. We believe this to be the first reported case showing peripheral nerve involvement.

Of particular interest was the relationship between blood pressure and cortical extract administration. On three separate occasions, cortical extract was withheld for variable periods. On each occasion, the systolic and diastolic pressures started downward two to three hours following the last injection and reached a maximum drop in seven to eight and one-half hours with the patient exhibiting fine tremors of the hands spreading to involve the face and general musculature and becoming coarser so that at the end of an hour they were quite coarse. On at least one of these occasions, Oct. 26, she developed subjective complaints of drowsiness and weakness. The blood pressure was permitted to continue downward from one to four hours before the administration of 10 c.c. of cortin intravenously. Response was manifested by an upward trend of systolic and diastolic pressures within one hour, requiring from eight to 16 hours to return to the original level while receiving 5 c.c. of cortin every three hours. The systolic and diastolic pressures responded similarly. Sodium and potassium determinations were not made owing to limitation of laboratory facilities.

It was noted that when parenteral cortin was alternated with cortate sublingually every three hours, the patient tended to maintain a somewhat lower daily blood pressure than when receiving 5 c.c. of cortin every three hours. At times the systolic pressure fell below 100 mm. and then tremors would appear. The latter could be made to disappear with supplementary parenteral doses of cortin. It was noticed that fall in blood pressure frequently coincided with marked elevation of temperature. Because cessation of tremulousness and rise in blood pressure followed administration of cortin fairly consistently, it was felt that hypotension and tremors were expressions of, at least, relative adrenal cortical insufficiency. It was thought that the signs and symptoms of cortical insufficiency constituted a non-specific reaction to sepsis and toxemia at first due to meningococcemia and later to gangrene and gross infection of the lower extremities. The patient was taken off cortin therapy on her fourth post-operative day and during the ensuing 30 days maintained her blood pressure, displaying no tremulousness or evidences of adrenal cortical insufficiency. It is inconceivable that destruction of the adrenals, in whole or in part, which could result in adrenal cortical hormone insufficiency for 25 days could be reversed within a period of four days following operation. Thus, hypotension and tremulousness were interpreted as expressions of relative adrenal insufficiency precipitated by sepsis and toxemia and aggravated by hemorrhagic adrenalopathy. As there appeared to be a fairly constant relationship between high fever and hypotension and

tremulousness, it was considered that altered physiology based on high fever with accelerated metabolic rate would be a major factor in precipitating relative cortical hormone insufficiency. Since one of the essential functions of the cortical hormone is considered to be that of catalyzing oxygen utilization,<sup>3</sup> an increased oxygen need would tend to make manifest latent impaired adrenal cortical function. It was felt that cortin extract administration played an important rôle in the survival of this patient and probably should be considered indispensable in the treatment of this syndrome.

Of some interest is the relatively high blood sugar present on admission. McGavack<sup>8</sup> reported a similar finding in his case which he explained on the basis of a trigger mechanism releasing adrenalin-like substances into the circulation with secondary elevation of blood sugar.

The blood sugar determination made at the height of a period during which the patient was exhibiting generalized coarse tremors read 120 mg. per cent so that hypoglycemia could not have been the cause. The tremors might be explained on a basis of secondarily impaired carbohydrate metabolism with resultant muscle weakness<sup>3</sup> and could be relieved by administration of cortin. The fact that the patient had adequate supplementary daily doses of sodium chloride suggested that loss of sodium was not a factor in the drop of blood pressure and appearance of tremors. Even if sodium was being lost, this is a relatively slow process<sup>1,5</sup> and would not become clinically manifest within eight hours. Furthermore, when cortate (desoxycorticosterone acetate) was being alternated with cortin, the patient maintained lower blood pressures than when maintained on cortin alone. Since desoxycorticosterone acetate is concerned with stabilizing electrolyte balance, the lower blood pressures present during its administration would militate against sodium loss as a cause of hypotension and tremors; however, it is true that there is a tendency toward irregular absorption with sublingual administration of cortate which must be taken into consideration.

#### SUMMARY

1. A case of Waterhouse-Friderichsen syndrome with recovery in a 17 year old white female exhibiting almost all the clinical criteria with the presence of meningococci in culture of the blood.

2. Present also were multiple areas of ectodermal necrosis and slough over the trunk and extremities with gangrene of the distal half of the right index finger and tip of the right middle finger. In addition, there was massive gangrene of the skin of the feet and lower legs requiring bilateral amputation and exhibiting microscopically arterial septic thrombi and arteriolar medial hypertrophy. In addition, there was present involvement of both ulnar nerves with hypesthesia, anesthesia and paralysis.

3. Hypotension and tremors were interpreted as evidences of relative adrenal cortical hormone insufficiency precipitated by sepsis and toxemia and aggravated by hemorrhagic adrenalopathy, and which could be induced during the course of illness by withholding cortin therapy.

4. The appearance of clinical manifestations was explained as due to altered physiology in which high fever with accelerated metabolic rate and resultant increased oxygen requirement made manifest latent adrenal cortical insufficiency.

5. Cortical extract is considered an indispensable adjunct of the treatment of Waterhouse-Friderichsen syndrome. Desoxycorticosterone acetate is probably ineffective.

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### ERRATUM

On page 242 of this issue an error occurred in the column headed "Cases." The corrected table is reprinted here.

TABLE III  
Duration of Symptoms at  
Examination at  
Clinic

Years	Cases
Less than 5	311
5-9	342
10-14	201
15-19	90
20 or more	74
Total	1,018*

\* In 17 cases duration of symptoms was indeterminate.

## EDITORIAL

### *THE EXPANDING INFLUENCE OF THE SCHOOLS OF MEDICINE*

IN THE reorganization of medical education in the United States which has occurred since the beginning of the century one may distinguish a period characterized by the integration of the medical schools with Universities, and by a tendency towards their isolation from the rest of the medical community. The dominant advances in this period have been the development of the medical sciences and of the clinical specialties.

The concentration of the schools upon the basic medical sciences and upon the problems of human disease led to alterations in the composition of the medical faculties and also for a time to a change in emphasis in medical education. It was early recognized that the faculty in the departments of the basic medical sciences must devote full time to their task if the work of these departments was to result in significant new contributions to medicine. Gradually the same reasoning came to be applied, in part at least, to the clinical departments. In all the major schools the number of junior full time clinical teachers and investigators has been increased and in a number of schools the heads of clinical departments are on a full time basis. In the selection of such full time personnel greater emphasis has usually been laid upon the man's aptitude for original investigation than upon his breadth of clinical knowledge and experience.

Inevitably the emphasis upon research led to some restriction of the interest of a major and most influential portion of the faculty in the problems of medical care in the home and in the physician's office, as well as in the increasing rôle of preventive medicine under city, state and federal auspices. In the teaching of medicine the emphasis was almost exclusively upon the structure and functions of the human body and its reaction to disease. The problems of the diseased individual, and the responsibility of the physician as his medical advisor received scant attention. There was in brief a tendency for medical schools to become isolated scientific institutes separated in interests from the practicing physicians and the health officers of their community.

This tendency to isolation did and, to some extent, still does exist; and it has tended to diminish the influence of the schools in a period of rapid changes in the organization of medicine in the United States. In the last twenty years, however, many factors have been operative which are bringing medical schools into closer relationship with the social problems of the sick and the medical problems of their communities and of the nation.

The development of welfare agencies, the growth of medical social service and perhaps most of all the infiltration into medical thinking of the psychiatric point of view have greatly altered clinical teaching. It is interesting to observe the new stress upon the patient as an individual and



the rediscovery in the schools of a fact well known to all successful general practitioners that patients have families and multiple other problems which affect their physical functions. More is being done to follow the patient into the home, and to integrate that portion of his medical care which he receives in the out-patient service or wards of the school with that which is afforded him by the clinics of the Health Department and by the general practitioner of his neighborhood. As progress is made in this direction the school not only extends its influence in the medical work of the community but can offer to its students a more complete view of the problem of adequate medical care for an individual.

The rapid growth of specialization in clinical medicine, combined with the standards set for specialists by the American Medical Association and the national societies of each specialty, has resulted in a greatly increased demand upon the medical schools for residencies and fellowships in the various special fields. The schools in their own interests as medical centers are attempting to develop active subdepartments in each clinical specialty. To do this successfully usually requires an increase in the number of available teaching beds. The solution of this problem has often been met by agreements which give to the school control of the free beds in voluntary or tax supported hospitals. The introduction of teaching and of school standards of medical care into such hospitals enables these institutions to obtain capable house officers and adjunct staff members who might otherwise not be attracted. The development by medical schools of such multiple hospital services is an increasing process. While often presenting great practical difficulties, it has the advantage of expanding the facilities of the school for postgraduate education and for research in new fields. Moreover, it brings the school into many new contacts with the community and greatly broadens its influence.

Another instance of the new extramural activities of the medical schools is to be seen in the close relationships recently developed between certain school departments of preventive medicine and the field work of the local Department of Health. Schools of medicine are usually called upon, moreover, to furnish representatives to all advisory councils connected with the medical programs which receive federal support. The integration of the school with the work of governmental health agencies, city, state and federal, has reciprocal aspects. The facilities of public health agencies are often supplemented by the school and on the other hand funds for certain types of clinical work and research in the schools are often provided by federal grants in aid.

Within very recent times, impelled by the urgency of the situation concerning the medical care of the veterans, the medical schools of this country have upon request assumed responsibility for nominating the attending physicians and consultants to the veterans hospitals in their vicinities. This association of the medical schools with the veterans hospitals has greatly assisted in the truly remarkable increase in prestige of these latter institu-

tions and has made it possible for them to procure many able younger physicians on a full time basis.

In the difficult situation in which the Medical Department of the United States Army now finds itself relative to procurement of specialists for its hospitals in this country, many faculty members of our schools as well as other qualified physicians are serving as consultants to army hospitals. If the army desires to establish more adequate educational advantages in its hospitals to serve as an incentive to recruitment, it is no doubt to the medical schools that it will turn for assistance.

The rapidly broadening influence of our medical schools in their communities and in the nation is evidence of their awareness of the changing conditions in organized medical care and of the increasing scope of their mission in medical education. If this influence is wisely used the schools will contribute greatly to the reorganization of medicine which is in process.

## REVIEWS

*X-Rays and Radium in the Treatment of Diseases of the Skin.* By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Director of the Department of Dermatology, New York Post-Graduate Medical School and Hospital, Columbia University, and ANTHONY C. CIPOLLARO, M.D., Assistant Professor of Dermatology and Assistant Director of the Department of Dermatology, New York Post-Graduate Medical School and Hospital, Columbia University. Contributor, HAMILTON MONTGOMERY, M.D., Associate Professor of Dermatology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, Rochester, Minnesota. Fourth edition, thoroughly revised. Cloth bound. Illustrated with 321 engravings and 4 colored plates. 668 pages; 15.5 × 24 cm. 1946. Lea & Febiger, Philadelphia. Price, \$10.00.

The appearance of a fourth edition of this book indicates that it is meeting a need. It is written primarily for dermatologists and roentgenologists but contains much information of value to internists.

The first 25 chapters are devoted to the history of x-ray and radium; to elementary electricity and the physics of radiation; to factors influencing tissue dosage and tissue recovery; to dangers associated with the administration of x-ray and radium therapy; to various technics of administering these rays; to modes of action of these rays on normal and abnormal tissues; to the effect of x-rays and radium on normal and abnormal tissues; and to acute and chronic radiodermatitis, stressing the great benefits of properly administered irradiation and the tragedy of improperly administered irradiation. These first chapters are written in simple, easily understood language and thoroughly cover all aspects of the modern concepts of radiation therapy. In a previous edition many of these chapters were revised by Dr. Edith H. Quimby, Associate Professor of Radiology, College of Physicians and Surgeons, Columbia University, a well known physicist who has devoted much time to correlating physical factors and biological results. Material added by Dr. Quimby has been retained in this edition.

The authors have stressed the dangers of x-rays and radium in unskilled hands, and to the need for specialized training before attempting to use these agents. They warn dermatologists not to place too much reliance on roentgen therapy. It is commendable that the tone of these chapters is conservatist.

The remaining 16 chapters are devoted to the clinical aspects of many skin diseases and to their treatment by x-rays and radium. In each disease the clinical aspects are adequately covered for a book of this type. The mode of action of the x-rays or radium is discussed. Indications for radiation therapy are enumerated. Advantages and disadvantages of radiation therapy are brought out. Technics and dangers are covered. Many treatises and textbooks on radiation therapy in the past have been sadly deficient in the detail description of technics. In this respect this volume, while still defective in certain instances, does represent a long step toward the goal of a compendium of roentgen technics with each carefully selected on the basis of clinical efficacy, and with each carefully described in detail.

The format is excellent. The numerous illustrations are well selected. The bibliography is quite complete and includes references of as late a date as 1943. The revised edition is recommended without reservation.

W. L. K.

*Diseases of the Endocrine Glands.* By HERMAN ZONDEK, M.D. Translated by CARL P. GILES, M.D. 496 pages; 23.5 × 15.5 cm. 1946. Williams & Wilkins Company, Baltimore. Price, \$11.00.

This is the fourth edition of a book which has already established itself as a valuable guide in the recognition and treatment of endocrine diseases. Dr. Zondek

has incorporated in it a majority of the developments in this field through the year 1943, and the completeness of his work is attested to by the 46 page bibliography at the end of the book. Of particular value are the numerous pictures of patients suffering from the various diseases, and the full length views emphasize the variations from normal body contour which typify a number of the endocrinopathies.

The first or general section of the book is devoted largely to the physiology and chemistry of the hormonal glands. The second or special section considers the various diseases attributable to endocrine dysfunction. In his preface, the author states that he has preferred to arrange the material according to diseases independent of their glandular origin because of the pluriglandular character of many of these disorders. In some instances this is helpful, while the understanding of other endocrine diseases would be aided by a more correlated discussion of the basic physiochemical aberrations producing the abnormalities.

This book is a valuable reference manual of endocrine disorders, and the demand which has resulted in this new edition is a tribute to its distinguished author.

J. Z. B.

*Victory Over Pain. A History of Anesthesia.* By VICTOR ROBINSON, M.D. 338 pages; 22 × 15 cm. 1946. Henry Schuman, New York. \$4.00.

This volume, appearing on the occasion of the centenary celebration of the first administration of ether, takes its place beside a host of similar publications off the press this year. The first six chapters, devoted largely to the very early use of pain-relieving herbs, contain little that has not been well covered elsewhere. The chapters on Humphry Davy and the little-known rôle of Henry Hickman in the development of gaseous anesthesia are, however, a valuable contribution. Five chapters are devoted to Long, Wells, Jackson and Morton and the ether controversy. These are followed by an interesting section of four chapters entitled, "The Reception of the Discovery in Europe." Contributions of the famous Nicoli Ivanovich Pirogoff to the "Great Discovery" are described, especially his development of the basic idea of rectal administration of ether vapors.

The classic literature on the development and acceptance of the theory of the relief of pain by chemical agents is adequately dealt with in the following chapters on the history of the discovery of chloroform anesthesia. Two chapters are dedicated to local anesthesia (Richardson and Koller). The succeeding sections deal with the history of the development of the technics of administration of anesthetics. Only those actively engaged in the practice of anesthesiology will be greatly interested in the details of complicated apparatus and technics of administration which are described.

C. J. C.

*Mongolism and Cretinism.* By CLEMENS E. BENDA. 310 pages; 24 × 15.5 cm. Grune & Stratton, New York, N. Y. 1946. Price, \$6.50.

Dr. Benda is the Director of the Wallace Research Laboratory for the Study of Mental Deficiency at the Wrentham State School, Wrentham, Mass. In this monograph he presents the material which he has accumulated in 10 years of intensive study of mongolism and cretinism. Throughout the various chapters which discuss the pathology and the manifestations of the two diseases, mongolism holds the dominant rôle, and the presentation of cretinism is, by the author's own statement, not intended to be complete. The possible steps to be taken from the obstetrical standpoint in the prevention of mongolism, a lengthy survey of the problem of the relation of the condition of the mother to this disease and a brief discussion of treatment complete the context of this work.

The author's views on mongolism are expressed in these statements: "Mongolism is the congenital type of hypopituitarism," and "The relationship between the mongoloid child and the pituitary dwarf is the same as that between the congenital thyroid aplastic cretin and the myxedematous child."

The prevailing view today is that mongolism is a result of a defective germ plasm and is not etiologically an endocrine dysfunction. Accordingly, the author's explanation of the disease demands closer inspection. He describes mongolism as the antithesis of acromegaly, a disease which has been shown to be due to an adenoma composed of the eosinophilic cells of the anterior lobe of the pituitary gland. The conspicuous increase in eosinophilic cells found in 54 per cent of his autopsy material he ascribes to so-called secretory stagnation, an explanation which is open to criticism. He supports his view as to the etiology of the disease by reporting good results obtained by treatment with thyrotropic hormone and thyroid substance. This method of treatment has received considerable notice recently in the lay press, and results in other clinics do not agree with the author's reports.

The chapters which discuss physical signs and symptoms and nervous and mental manifestations are instructive. The inclusion of more illustrations of the facies and other physical characteristics of the diseases would be helpful. The index is complete, and the format of the book is unusually good.

This book has already precipitated widespread discussion. Mongolism is a tragic occurrence which has darkened many lives, and there are bound to be false enthusiasms aroused by the dogmatic manner in which Dr. Benda presents his theories as to the etiology and treatment of the disease.

J. Z. B.

#### BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Hypo-Metabolism.* By ESBEN KIRK, M.D., and SVEN ANCHER KVORNING, M.D. 83 pages; 24 × 15.5 cm. 1946. Einar Munksgaard, Copenhagen. Price, Dan Cr. 7.25.

*The Nervous Child.* Fifth Edition. By H. C. CAMERON. 252 pages; 19 × 12.5 cm. 1946. Oxford University Press, New York, London.

*Health Insurance in the United States.* By NATHAN SINAI, Dr.P.H., ODIN W. ANDERSON, and MELVIN L. DOLLAR, School of Public Health, University of Michigan. 115 pages; 21.5 × 14 cm. 1946. The Commonwealth Fund, New York, N. Y. Price, \$1.50.

*Myasthenia Gravis.* By DR. ADALBERTO R. GOÑI. Translated by GEORGIANNA SIMMONS GITTINGER. 112 pages; 23.5 × 16 cm. 1946. The Williams & Wilkins Company, Baltimore.

*The X-Ray Treatment of Accessible Cancer.* By D. WALDRON SMITHERS, M.D., D.M.R. Former Director Dept. Radiotherapy, St. Thomas Hospital, London. 147 pages; 27.5 × 19 cm. 1946. The Williams & Wilkins Company, Baltimore. Price, \$8.50.

*Penicillin in Neurology.* By A. EARL WALKER, M.D., Assoc. Prof. Neurological Surgery, Univ. of Chicago, and HERBERT C. JOHNSON, M.D. 202 pages; 24 × 14 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, \$5.00.

## COLLEGE NEWS NOTES

### ADDITIONAL LIFE MEMBERS OF THE COLLEGE

The College is highly gratified to announce that the following Fellows have become Life Members:

Dr. George L. Steele, F.A.C.P., Springfield, Mass., December 18, 1946  
Dr. John I. Marker, F.A.C.P., Davenport, Iowa, December 20, 1946  
Dr. Lorenzo D. Massey, F.A.C.P., Osceola, Ark., December 23, 1946  
Dr. Murray De Armond, F.A.C.P., Indianapolis, Ind., December 30, 1946  
Dr. Joseph F. Hamilton, F.A.C.P., Memphis, Tenn., December 30, 1946  
Dr. E. Cooper Cole, F.A.C.P., Toronto, Ont., Can., December 31, 1946  
Dr. Felix R. Park, F.A.C.P., Tulsa, Okla., December 31, 1946  
Dr. Samuel Goodman, F.A.C.P., Tulsa, Okla., January 6, 1947  
Dr. Harold K. Eynon, F.A.C.P., Collingswood, N. J., January 13, 1947  
Dr. William LeRoy Dunn, F.A.C.P., Washington, D. C., January 14, 1946  
Dr. Evert Abram Bancker, F.A.C.P., Atlanta, Ga., January 17, 1947  
Dr. Glenn Edward Drewyer, F.A.C.P., Glenwood Springs, Colo., January 17, 1947  
Dr. Carl H. Fortune, F.A.C.P., Lexington, Ky., January 17, 1947  
Dr. Hugh E. Kiene, F.A.C.P., Providence, R. I., January 17, 1947  
Dr. Isidore Lattman, F.A.C.P., Washington, D.C., January 17, 1947  
Dr. Lemuel C. McGee, F.A.C.P., Wilmington, Del., January 17, 1947  
Dr. Matthew Molitch, F.A.C.P., Atlantic City, N. J., January 17, 1947  
Dr. Frank F. D. Reckord, F.A.C.P., Harrisburg, Pa., January 17, 1947  
Dr. Charles Windwer, F.A.C.P., Brooklyn, N. Y., January 17, 1947  
Dr. Samuel C. Arnett, Jr., F.A.C.P., Lubbock, Tex., January 18, 1947  
Dr. Frank C. Clifford, F.A.C.P., Toledo, Ohio, January 18, 1947  
Dr. John B. D'Albora, F.A.C.P., Brooklyn, N. Y., January 18, 1947  
Dr. Richard F. Herndon, F.A.C.P., Springfield, Ill., January 18, 1947  
Dr. Charles W. McClure, F.A.C.P., Boston, Mass., January 18, 1947  
Dr. Ernest G. McEwen, F.A.C.P., Evanston, Ill., January 18, 1947  
Dr. Mary M. Spears, F.A.C.P., Philadelphia, Pa., January 21, 1947  
Dr. William Stein, F.A.C.P., New Brunswick, N. J., January 21, 1947  
Dr. Kenneth Taylor, F.A.C.P., New York, N. Y., January 21, 1947  
Dr. Gordon B. Wilder, F.A.C.P., Anderson, Ind., January 21, 1947

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The American College of Radiology and the Philadelphia Roentgen Ray Society will offer postgraduate courses in radiology, March 30–April 4, in Philadelphia. Registration is limited to 100. Preference will be given first to radiologists who served in World War II; then to qualified applicants who could not be admitted to last year's course in Philadelphia. Inquiries may be addressed to American College of Radiology, Postgraduate Courses, 20 N. Wacker Drive, Chicago 6, Ill.

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The Sixteenth Annual Spring Clinical Conference of the Dallas Southern Clinical Society will occur March 17–20 in the Hotel Adolphus, Dallas. Drs. Willard O. Thompson, F.A.C.P., Chicago, and Julius L. Wilson, F.A.C.P., New Orleans, will be among the guest speakers.

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The 1947 Annual Meeting of the Minnesota State Medical Association will be held in Duluth, June 30–July 2.

## 1947 MEMBERSHIP ROSTER DISTRIBUTED

The Board of Regents authorized the publication of a complete Directory of The American College of Physicians during 1946. It became apparent subsequently that because of the scarcity of paper, and the difficulties which our printer encountered with respect to labor, the publication of a complete Directory would be exorbitant in cost and unpredictable as to date of publication. The Executive Committee of the Board of Regents therefore authorized the publication of a Membership Roster in its place. It was found that labor problems delayed the preparation and completion of this Roster so that its title has been changed to "Membership Roster—1947." The Roster has now been mailed to all members of the College in good standing. If any have failed to receive their copies, they are requested so to inform the Executive Secretary of the College. Also, it is desired that the Executive Secretary be notified of any corrections or omissions in the Roster listings.

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 PROPOSALS OF CANDIDATES

In submitting the proposals of candidates for Membership in the College, it is requested that the proposers keep in mind that proposals must be filed at least thirty days in advance of action by the Committee on Credentials. This Committee will meet next on March 30 and again on April 27, 1947. A third meeting will occur at some date in the autumn of 1947. The Board of Regents will meet April 27, during the Annual Session of the College in Chicago.

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 REGIONAL MEETINGS OF THE COLLEGE
*New England, January 28, 1947*

A Regional Meeting of the College for Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont, was held at Hanover, N. H., January 28, under the general chairmanship of Dr. Harry T. French, Governor for New Hampshire, with the coöperation of Governors Alex. M. Burgess, Eugene H. Drake, Paul K. French, Chester S. Keefer, and Thomas P. Murdock. Dr. Sven M. Gundersen, F.A.C.P., was chairman of the local committee on arrangements. The program was as follows: Address of Welcome, Rolf C. Syvertsen, M.D., Dean of Dartmouth Medical School; Newer Methods of Treatment of Thyrotoxicosis, Robert H. Williams, M.D., Boston; Sympathetic Neuro Secretion and Heart Disease, Wilhelm Raab, M.D., F.A.C.P., Burlington; Interruption of the Sympathetic Nervous System in Relation to Trauma, M. Dawson Tyson, M.D., Hanover; Nutrition Problems in Medical and Surgical Practice, Charles S. Davidson, M.D., Boston; Multiple Myelomata, Herman A. Lawson, M.D., F.A.C.P., Providence; Cutaneous Diphtheria, Averill A. Liebow, M.D., New Haven; Respiratory Diseases Treated with Streptomycin, Maxwell Finland, M.D., F.A.C.P., Boston; Significance of Liver Function Tests, Franz J. Ingelfinger, M.D., Boston; Biliary Cholesterosis, Russell S. Bray, M.D., F.A.C.P., Providence; The Rôle of Endocrinology in Urology, William L. McLaughlin, M.D., Hanover; The Clinical Use of the Oximeter, John Abajian, Jr., M.D., Burlington; Objective Methods for the Evaluation of Bronchodilator Drugs in the Treatment of Bronchial Asthma, John J. Curry, M.D., Boston; The Effects of Intravenous Fluids on Plasma Volume, Hematocrit, Plasma Proteins and Urinary Output in Convalescent Patients, William J. H. Fischer, M.D., and R. O. Bowman, Ph.D., Providence; A Method of Determining the Volume of the Coronary Bed, Julius Gottlieb, M.D., F.A.C.P., Lewiston; Evaluation of the Treatment of Rheumatoid Arthritis, Marian Ropes, M.D., Boston; The Use of Sodium Succinate in the Treatment of

Acute Phenobarbital Poisoning, Richard H. Barrett, M.D., Hanover; The Morbid Interplay of Endocrines, William T. Salter, M.D., New Haven. Following a reception and banquet, Dr. David P. Barr, President of the College, addressed the members and their guests.

*Eastern Pennsylvania, Southern New Jersey, and Delaware, February 7, 1947*

The ninth annual round-up of College members in eastern Pennsylvania, joined by members from Delaware and southern New Jersey, took place on February 7 at Philadelphia. Governor Edward L. Bortz, assisted by Governors Lewis B. Flinn and George H. Lathrope and a committee of twenty Fellows from the area, acted as general chairman of the meeting. Distinguished guests included officers of the College and of medical schools and organizations of Philadelphia. Attendants were invited to participate during the morning in the program of the postgraduate course on Growth, Isotopes, and Tumor Formation, at the Lankenau Hospital Research Institute. The following papers by Philadelphia physicians were presented at the afternoon session: John Q. Griffith, Jr., M.D., F.A.C.P., Hypertension; Malcolm W. Miller, M.D., F.A.C.P., Anti-histamine Therapy; Louis B. Laplace, M.D., F.A.C.P., The Ageing Heart; Samuel B. Hadden, M.D., F.A.C.P., The Genesis of the Neuroses; Henry F. Lee, M.D. (by invitation), Experimental Studies with Streptomycin; Henry R. Carstens, M.D., F.A.C.P., The Medical Program for Veterans.

A reception and dinner at the Warwick Hotel followed the day's program. The meeting was a most successful one.

*Virginia, February 19*

An excellent program for the Virginia Regional Meeting was arranged, under the Governorship of Dr. J. Edwin Wood, Jr., by Dr. Charles M. Caravati, F.A.C.P., Richmond, and Dr. James F. Waddill, F.A.C.P., Norfolk, chairman and secretary, respectively, of the Virginia group. The meeting consisted of a scientific program in the afternoon, conducted at the McGuire General Hospital, followed by refreshments and dinner at the Richmond Academy of Medicine. The scientific papers were: Elam C. Toone, Jr., M.D., F.A.C.P., Rheumatoid Spondylitis; William B. Porter, M.D., F.A.C.P., Ductus Arteriosus: Diagnosis and Surgical Indications; Sidney G. Page, Jr., M.D. (Associate), Streptomycin in Brucellosis; T. Dewey Davis, M.D., F.A.C.P., Xanthomatous Biliary Cirrhosis; Henry St. George Tucker, Jr. (by invitation), Nitrogen Mustard in Malignant Lymphomas; Joseph R. Kriz, M.D., F.A.C.P., Reticulo-endotheliosis; J. Powell Williams, M.D. (by invitation), Liquefying Nodular Panniculitis; Wyatt E. Royce, M.D. (by invitation), Pneumoperitoneum in Tuberculosis; J. O. Burke, M.D. (by invitation), Vagotomy for Peptic Ulcer; Reno R. Porter, M.D. (Associate), Penicillin in Cardiovascular Syphilis; Benedict Nagler, M.D. (by invitation), Demonstration of Neurological Cases.

Dr. Edward L. Bortz, Vice Chairman of the Board of Governors, Governor for Eastern Pennsylvania, and Chairman of the Committee on Postgraduate Courses, and Mr. E. R. Loveland, Executive Secretary, were the guest speakers.

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Dr. George Parkman Denny, F.A.C.P., Boston, formerly Colonel in the Medical Corps, A.U.S., has been awarded the Legion of Merit. Mention is made in the citation of the highest standards of medical service which were attained in hospitals of the First Service Command, to which Dr. Denny was Medical Consultant, January 1944 to October 1945.



Colonel Wesley C. Cox, (MC), USA, F.A.C.P., has been assigned to the post of Chief of the Army Industrial Hygiene Laboratory at Edgewood Arsenal, Md., with offices in the Surgeon General's office. Dr. Cox was awarded the Legion of Merit, the Army Commendation Ribbon, a Panamanian Decoration, and was named to the Order of Basco Nunez de Balboa, for his work on control of malaria in the Panama Department and Zone during the past seven years.

Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, has been awarded the Legion of Merit for "exceptionally meritorious service as commanding officer, Percy Jones General Hospital, from June 15, 1942, to April 13, 1943. For conspicuous performance as an organizer, administrator, and professional surgeon, culminating in the establishment of the country's largest Army Hospital Center, which has been unexcelled for eminent achievement in military medicine."

Edward C. Reifenshtein, Jr., F.A.C.P., New York, N. Y., formerly Harvard Medical School Research Fellow at the Massachusetts General Hospital, has been appointed Research Consultant to the Sloan-Kettering Institute for Cancer Research at the Memorial Hospital Cancer Center, New York City. At the Sloan-Kettering Institute, he will carry on clinical research on the relation of glandular disturbances to cancer. He will also continue as Secretary and Editor of the Transactions of the Conferences on the Metabolic Aspects of Convalescence.

Dr. J. Robert Willson, formerly Assistant Professor at the University of Chicago, has been appointed Professor and Head of the Department of Obstetrics and Gynecology in the Temple University School of Medicine and Hospital. Dr. Valy Menkin, formerly engaged in research at the Harvard Medical School and at Duke University, has been appointed Associate Professor of Experimental Pathology.

Temple University has received from the National Cancer Institute a grant of \$10,000 for a study of the relation of cellular injury to the development of repair and neoplastic tendencies, as well as a grant of \$20,750 a year from the U. S. Public Health Service in support of physical and physiological studies of the heart and circulation.

#### RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to January 13, 1947 inclusive):

Robley D. Bates, Jr., Richmond, Va. (Major, MC, AUS)  
 Orin J. Farness, Tucson, Ariz. (Lt. Col., MC, AUS)  
 W. Lee Hart, Dallas, Tex. (Brig. Gen., MC, USA)  
 T. Haynes Harvill, Dallas, Tex. (Lt. Comdr., MC, USNR)  
 Ng. William Hing, Flint, Mich. (Capt. MC, AUS)  
 Herman Lande, New York, N. Y. (Col. MC, AUS)  
 Arthur G. Lueck, Des Moines, Iowa (Lt. Comdr., MC, USN)  
 Hertel P. Makel, Moorestown, N. J. (Col. MC, USA)  
 David M. Marcley, Amarillo, Tex. (Lt. Comdr., MC, USNR)  
 L. Tillman McDaniel, Boston, Mass. (Major, MC, AUS)  
 John E. Moss, Memphis, Tenn. (Lt. Comdr., MC, USN)  
 George P. Robb, New York, N. Y. (Lt. Col., MC, AUS)  
 John C. Ruddock, Los Angeles, Calif. (Capt., MC, USNR)  
 William G. Sauer, Rochester, Minn. (Lt., MC, AUS)  
 Eugene M. Schloss, Philadelphia, Pa. (Major, MC, AUS)

# TENTATIVE PROGRAM THE AMERICAN COLLEGE OF PHYSICIANS

Twenty-Eighth Annual Session

CHICAGO, ILL.

April 28-May 2, 1947

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G. Karl Fenn	}	St. Luke's Hospital
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Robert Brown, Medical Director, St. Luke's Hospital  
Eben Carey, Curator of Medical Exhibits, Museum of Science and Industry  
Warren Cole, Assistant Dean, University of Illinois College of Medicine  
Miss Henrietta Froehle, Director of Nursing, Presbyterian Hospital  
Stanley Gibson, Medical Director, Children's Memorial Hospital  
R. Wendell Harrison, Dean, Division of Biological Sciences, University of Chicago  
Mr. Luther Hammond, Superintendent, Passavant Memorial Hospital  
Mr. Fred A. Hertwig, Warden, Cook County Hospital  
William G. Hibbs, Medical Director, Presbyterian Hospital  
Morris Kreeger, Superintendent, Michael Reese Hospital  
Major Lenox R. Lohr, Director, Museum of Science and Industry  
Miss Mildred Lorentz, Director of Nursing, Michael Reese Hospital  
Mr. Leo Lyons, Director, St. Luke's Hospital  
Sister Mary Therese, R.S.M., Superintendent, Mercy Hospital  
Miss Madeleine M. McConnell, Director, School of Nursing, St. Luke's Hospital  
Miss Veronica Miller, Superintendent, Henrotin Hospital  
Mr. E. J. Millizen, Administrator, Research and Educational Hospitals  
Ole Nelson, Medical Director, Cook County Hospital  
Mr. Daniel Catton Rich, Director, Art Institute of Chicago  
James J. Smith, Dean, Loyola University School of Medicine

## HONORARY COMMITTEE

## Living Past Presidents

Ernest E. Irons	James Alex. Miller
James E. Paullin	Jonathan C. Meakins
Roger I. Lee	George Morris Piersol
O. H. Perry Pepper	Francis M. Pottenger, Sr.
William J. Kerr	S. Marx White
James H. Means	Sydney R. Miller
Ernest B. Bradley	John H. Musser

Charles F. Martin

## INVITATION

The City of Chicago, its medical profession, institutions and hospitals, in extending a most cordial invitation to the members of The American College of Physicians

to attend the Twenty-Eighth Annual Session, is happy indeed to offer the courtesies of the City and the facilities of its institutions to so distinguished an organization.

Chicago is the home of four Class A medical schools: (1) The University of Chicago, started through the efforts of William Rainey Harper shortly after the famous World's Fair of 1893 and located on the very territory of this Fair, is a school now internationally known, particularly recently as the place at which began the initial experiments in the atom bomb. It is the only school in Chicago which has its hospitals staffed by full-time medical men. (2) Northwestern University was begun through the efforts of Nathan Smith Davis, founder of the American Medical Association and pioneer worker in raising the standards of medical education. This school is now building a tremendous institution on the near north side within easy reach of downtown Chicago. (3) The University of Illinois, owned and operated by the State of Illinois, represents one of the finest state institutions in the country. Teaching is under the direction of men devoting all or a great share of their time to this project, buffered and complemented by a large faculty of part-time and volunteer workers. The plans of this school call for the building of several new hospitals and the steady expansion of facilities for the care of the sick of the State of Illinois. Rush Medical College, the famous school known throughout the world for its fine faculty and progressive ideas in medical education, and formerly affiliated with the University of Chicago, is now, through the Presbyterian Hospital and the Central Free Dispensary, closely affiliated with the University of Illinois so that the teaching begun in this pioneer institution which was chartered before the City of Chicago, continues as before under the watchful eye and close guidance of a great university. (4) Loyola University is located in close proximity to the great Cook County Hospital. This institution has a plan for expansion of its physical and educational plant and the building of a large hospital.

Chicago is the home of the American Medical Association, founded through the efforts of members of the faculties of Rush Medical College and Northwestern University Medical School, and of The American College of Surgeons, which continues its early efforts in raising the standards of surgical and hospital practice as it did under the inspiration of a great executive, Franklin Martin.

Chicago is the center of a tremendous industrial community. During the war her facilities were taxed to the utmost, but her hospitality was given freely and in fine measure to men of all ranks and in all branches of the Service. The Chicago Service Men's Center under the capable direction of Mayor and Mrs. Edward J. Kelly was the meeting place of huge numbers of men from the largest naval center in the World, Great Lakes, down through Fort Sheridan, the Glen View air field, Camp Grant, Navy Pier, Chanute Field, and to thousands of service men passing through the city. During the war Chicago was headquarters for the Sixth Service Command and is now headquarters for the Fifth Army.

Aside from the medical advantages and attractions of Chicago, there are other features of which this city is very proud: The Art Institute; the Museum of Science and Industry; Field Museum; Shedd Aquarium; Adler Planetarium; Chicago Historical Society; Hull House, made famous by Jane Addams; Chicago Symphony Orchestra; the Crerar Library, which is one of the largest medical libraries in the world; the "loop" with its excellent shops, stores, restaurants and theaters, and the magnificent lake front close at hand.

It is the hope of those locally responsible for the Twenty-Eighth Annual Session of the College that in accepting this invitation you will take the opportunity to visit our world famous medical and civic institutions and return home professionally and socially stimulated and satisfied that you have gained a respite from the daily duties of busy practitioners, and able to keep pace with a world that is changing almost too rapidly.

## GENERAL INFORMATION

### GENERAL HEADQUARTERS

Palmer House  
15 E. Monroe St.

Registration headquarters, information bureau, technical exhibits, general sessions, morning lectures and panel discussions.

The Palmer House will be the headquarters hotel for Officers, Regents and Governors, and so far as facilities permit, will accommodate other members and guests of the College. Other official hotels include the Bismarck, Chicagoan, Congress, Morrison, Sherman and Stevens. A number of other hotels are also named below but none of these has officially promised accommodations.

The Congress Hotel will be the official headquarters of the technical exhibitors, who may make their reservations direct by communicating with Mr. Daniel Amico, Sales Manager.

Officers, Regents, Governors, Speakers and Clinicians on the Program should apply for hotel accommodations directly through Mr. E. R. Loveland, Executive Secretary, The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa. All other physicians and guests should apply for hotel accommodations through

The Housing Committee  
The American College of Physicians  
c/o Chicago Convention Bureau  
33 N. La Salle St.  
Chicago 2, Ill.

State clearly date and time of anticipated arrival and hotel of first, second and third choice, and range of rates acceptable. A reservation card will accompany the Official Program.

### PARTIAL LIST OF CHICAGO HOTELS

#### DOWNTOWN

Hotel	Rates*	
	Single	Double
PALMER HOUSE		
15 E. Monroe St.	3.85	5.50 up
Bismarck		
171 W. Randolph St.	2.75 & 3.75	5.25
Blackstone		
Michigan Ave. at Balbo Ave.	4.00	7.00
Chicagoan		
67 W. Madison St.	2.75	4.40
Congress		
500 S. Michigan Ave.	3.50	6.00
La Salle		
Madison and La Salle Sts.	2.00 & 2.75	3.00 & 4.40
Morrison		
79 W. Madison St.	2.75	4.40
Sherman		
106 W. Randolph St.	2.75	4.40
Stevens		
720 S. Michigan Ave.	3.25 up	5.00 up

\* Subject to change, if OPA ceilings removed before this meeting.

## NORTH SIDE

Allerton		
701 N. Michigan Ave.	1.75 & 2.75	3.00 & 4.50
Drake		
Walton Pl. at Michigan Ave.	4.00 up	7.00 up
Edgewater Beach		
5349 Sheridan Rd.	4.40 & 5.50	6.60 & 7.70
Knickerbocker		
163 E. Walton Pl.	3.50	5.00

Hotel facilities are limited; members are urged to use double rooms, due to comparative shortage of single rooms. Reservations starting on Sunday, the largest checkout day, receive some preference by the hotels. Physicians should mention specifically the fact that reservations are being made in connection with the Annual Session of The American College of Physicians.

## WHO MAY REGISTER—

- (a) All members of The American College of Physicians in good standing for 1947 (dues, if not paid previously, may be paid at the Registration Bureau).
- (b) All newly elected members.
- (c) Senior and graduate medical students pursuing courses at the University of Chicago, University of Illinois, Northwestern University and Loyola University, without registration fee, upon presentation of matriculation cards or other evidence of registration at these institutions; exhibits, general sessions and morning lectures.
- (d) Members of the staff, including internes, of the hospitals participating in the program, without registration fee, upon presentation of proper identification; exhibits, general sessions and morning lectures.
- (e) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.
- (f) Qualified physicians who may wish to attend this Session as visitors; such physicians shall pay a registration fee of \$12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

**Registration Bureau**—While official registration will start on Monday morning, April 28, temporary registration facilities will be open on the 4th Floor of the Palmer House on Sunday, April 27, from 2:30 to 5.00 in the afternoon. The regular Registration Bureau through the week will be open from 8:30 A.M. to 5:45 P.M.

**Registration Blanks for All Clinics and Panel Discussions** are sent with the program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

**Bulletin Boards** for special announcements will be located near the Registration Bureau on the 4th Floor of the Palmer House.

**Transportation**—Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the Meeting.



**The General Business Meeting** of the College will be held at 2:00 P.M., Thursday, May 1, immediately preceding the afternoon scientific session. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors and the annual reports will be received from the Secretary General, Executive Secretary and Treasurer. The President-Elect, Dr. Hugh J. Morgan, Nashville, Tenn., will be inducted into office.

**Board and Committee Meetings**—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

**A dinner meeting of the Board of Regents and of the Board of Governors** will be held in the Crystal Room, 3rd Floor of the Palmer House, Sunday, April 27, at 7 P.M.

### COMMITTEE ON CREDENTIALS

Sunday, April 27, 9:15 A.M. .... Room 403, 4th Floor

### BOARD OF REGENTS

Palmer House, Room 9, 3rd Floor

Sunday, April 27, 2:00 P.M.

Tuesday, April 29, 12:00 M.\*

Friday, May 2, 12:00 M.\*

### BOARD OF GOVERNORS

Palmer House, Room 9, 3rd Floor

Monday, April 28, 5:00 P.M.

Wednesday, April 30, 12:00 M.\*

\* Buffet luncheon served.

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### SPECIAL FEATURES

**Monday, April 28, 1947**

**A SPECIAL FEATURE OF ENTERTAINMENT** for everyone in attendance at the Session has been arranged by the Entertainment Committee. It will probably be the presentation of the Play, "HARVEY," starring Joe E. Brown. A special program will be announced and published later.

**Wednesday, April 30, 1947**

**THE ANNUAL CONVOCATION OF THE COLLEGE**—8:30 P.M., Grand Ballroom, Palmer House. All members of the College and their families, and those of the public who are interested, are invited. All physicians elected Fellows of the College since the 1946 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents, Governors and new Fellows to be inducted, are requested to assemble in the Red Lacquer Room, fourth floor, Palmer House, at 7:45 P.M., preparatory to the formation of the procession. They will be conducted to their seats by the Marshal of the Convocation, Dr. T. Grier Miller, promptly at 8:30 P.M. It is suggested that all appear in evening clothes

The Convocation ceremony will include the President's Address and a Convocational Oration, "Can UNESCO Succeed?" by Dr. George D. Stoddard, President, The University of Illinois, United States Delegate to the First General Conference of United Nations Educational, Scientific and Cultural Organization. The award of the John Phillips Memorial Medal for 1947 will be made and the recipients of Research Fellowships of the College for 1947 will be announced. The newly elected Fellows will be presented by the Secretary General, Dr. George Morris Piersol, and after subscribing to the Fellowship Pledge, will be inducted by the President. The President's Reception and Dance will follow immediately after the Convocation in the Red Lacquer Room. All members and their guests are requested to pass along the receiving line.

**Thursday, May 1, 1947**

**THE ANNUAL BANQUET** will be held in the Grand Ballroom of the Palmer House at 8:00 o'clock. Franklyn Price Snyder, President of Northwestern University, will be the speaker of the evening.

All members of the College, physicians of Chicago and surrounding area, visitors attending the Session, guests and friends, with their families, are cordially invited. Table reservations for groups may be arranged. Orchestral music will be furnished, and the evening has been planned as a most delightful occasion. Tickets should be purchased at the Registration Bureau by Wednesday afternoon, so that adequate preparations can be consummated.

#### **PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN**

The Ladies' Entertainment Committee has prepared an interesting program for the visiting women which it hopes will be keenly enjoyed by all. These guests are requested to register at the Ladies' Headquarters in the Ballroom Foyer, 4th Floor of the Palmer House, on their arrival in Chicago. Programs will be available at registration, as will also maps, lists of theaters, shops, restaurants and places of interest in and about Chicago.

The Ladies' Committee will be ready to start registering on Sunday afternoon, April 27. Certain of the entertainment features may be somewhat limited in accommodations and, therefore, early registration is requested.

The Ladies' Program includes a welcoming tea at the Woman's Athletic Club, a tour of the south side of Chicago along the great Outer Drive, passing by the Shedd Aquarium, Field Museum, Soldier Field, Adler Planetarium, the Midway, the campus of the University of Chicago, terminating at the Museum of Science and Industry in Jackson Park where the group will be the guests of the Director of the Museum. Buses will be provided for this tour and will leave at specified time from the Palmer House and the Stevens Hotel. The tour will be followed by a luncheon at a nearby hotel and a book review by one of Chicago's famous reviewers.

The Committee has arranged for a fashion show and breakfast at the Drake Hotel by Marshall Field and Company, and also a special exhibit-lecture-tea at the Art Institute of Chicago.

On Monday evening the women will be guests of the Local Entertainment Committee. Tuesday evening is free for theater parties or private entertainment. On Wednesday evening the Convocation will be held in the Ballroom of the Palmer House, followed by the President's Reception and Dance. On Thursday evening will be held the gala Banquet with Franklyn Bliss Snyder, President of Northwestern University, as the speaker.

**THE TECHNICAL EXHIBIT** will be located in the Exhibition Hall, fourth floor of the Palmer House. Exhibitors are admitted by invitation; all booths were

promptly subscribed for, some exhibitors failing to obtain space due to lateness of application.

The American College of Physicians conducts its Technical Exhibits according to the highest standards. All irrelevant products have been eliminated and only firms are invited who present a group of approved products of scientific interest to internal medicine and its allied specialties. Physicians will appreciate the difference between our Exhibit and general medical exhibits elsewhere, where frequently many products irrelevant to the actual practice of medicine are displayed and where questionable methods of selling are permitted. The College enjoys the full cooperation of its exhibitors and of its members. Exhibitors are making a special effort, under current difficult conditions, to present to the members of the College new and improved developments in their respective fields. Here, conveniently available, will be displayed the leading medical books, pharmaceuticals, apparatus and appliances, and many other products or services, making up much of the armamentarium of medical practice. These exhibitors and their displays merit your courteous attention, not only because of their educational value but because of their contributions to the support of the Annual Sessions of the College.

Special intermissions have been arranged, providing additional time for the inspection of the Exhibits.

#### 1947 EXHIBITORS

Abbott Laboratories, North Chicago, Ill.  
 Allergia Coverings Co., Medway, Mass.  
 American Hospital Supply Corporation, Evanston, Ill.  
 Ames Company, Inc., Elkhart, Ind.  
 Appleton-Century Company, D., New York, N. Y.  
 Arlington Chemical Company, The, Yonkers, N. Y.  
 Armour Laboratories, The, Chicago, Ill.  
 Ayerst, McKenna & Harrison Limited, New York, N. Y.  
 Baum Co., Inc., W. A., New York, N. Y.  
 Beck-Lee Corporation, Chicago, Ill.  
 Becton, Dickinson & Co., Rutherford, N. J.  
 Bilhuber-Knoll Corp., Orange, N. J.  
 Blakiston Company, The, Philadelphia, Pa.  
 Borden Company, The, New York, N. Y.  
 Bristol Laboratories, Inc., New York, N. Y.  
 Burdick Corporation, The, Milton, Wis.  
 Burroughs Wellcome & Co. (U.S.A.), Inc., New York, N. Y.  
 Cambridge Instrument Co., Inc., New York, N. Y.  
 Cameron Surgical Specialty Company, Chicago and New York  
 Ciba Pharmaceutical Products, Inc., Summit, N. J.  
 Collins, Inc., Warren E., Boston, Mass.  
 Cream of Wheat Corporation, The, Minneapolis, Minn.  
 Davies, Rose & Company, Limited, Boston, Mass.  
 Davis Company, F. A., Philadelphia, Pa.  
 Devereux Schools, Devon, Pa.  
 Dietene Company, The, Minneapolis, Minn.  
 Doak Company, Inc., Cleveland, Ohio  
 Doho Chemical Corporation, The, New York, N. Y.  
 Fleet Company, Inc., C. B., Lynchburg, Va.  
 General Electric X-Ray Corporation, Chicago, Ill.  
 Gerber Products Company, Fremont, Mich.  
 Grune & Stratton, Inc., New York, N. Y.

Heinz Co., H. J., Pittsburgh, Pa.  
Hoeber, Inc., Paul B., New York, N. Y.  
Hygeia Nursing Bottle Co., Inc., The, Buffalo, N. Y.  
Jones Metabolism Equipment Co., Chicago, Ill.  
Kellogg Company, Battle Creek, Mich.  
Kinney and Sons, Inc., H. W., Columbus, Ind.  
Knox Gelatine Co., Inc., Chas. B., Johnstown, N. Y.  
LaMotte Chemical Products Company, Baltimore, Md.  
Lea & Febiger, Philadelphia, Pa.  
Lederle Laboratories, Inc., Pearl River, N. Y.  
Liebel-Flarsheim Co., The, Cincinnati, Ohio  
Lilly and Company, Eli, Indianapolis, Ind.  
Lippincott Company, J. B., Philadelphia, Pa.  
Macmillan Company, The, New York, N. Y.  
Maltine Company, The, New York, N. Y.  
McNeil Laboratories, Inc., Philadelphia, Pa.  
Mead Johnson & Company, Evansville, Ind.  
Medical Bureau, The, Chicago, Ill.  
Medical Case History Bureau, New York, N. Y.  
Medical Fabrics, Inc., Paterson, N. J.  
Medical Film Guild, New York, N. Y.  
Medical Protective Company, The, Fort Wayne, Ind.  
Merck & Co., Inc., Rahway, N. J.  
Merrell Company, The Wm. S., Cincinnati, Ohio  
Mosby Company, The C. V., St. Louis, Mo.  
Oxford University Press, New York, N. Y.  
Parke, Davis & Company, Detroit, Mich.  
Patch Company, The E. L., Boston, Mass.  
Picker X-Ray Corporation, New York, N. Y.  
Procter & Gamble Company, The, Cincinnati, Ohio  
Rare Chemicals, Inc., Harrison, N. J.  
Sanborn Company, Cambridge, Mass.  
Sandoz Chemical Works, Inc., New York, N. Y.  
Saunders Company, W. B., Philadelphia, Pa.  
Schenley Laboratories, Inc., New York, N. Y.  
Schering Corporation, Bloomfield, N. J.  
Searle & Co., G. D., Chicago, Ill.  
Sharp & Dohme Incorporated, Philadelphia, Pa.  
Smith, Kline & French Laboratories, Philadelphia, Pa.  
Squibb & Sons, E. R., New York, N. Y.  
Stearns & Company, Frederick, Detroit, Mich.  
Swift & Company, Chicago, Ill.  
Taylor Instrument Companies, Rochester, N. Y.  
U. S. Vitamin Corporation, New York, N. Y.  
University of Chicago Press, The, Chicago, Ill.  
Upjohn Company, The, Kalamazoo, Mich.  
Varick Pharmacal Company, Inc., New York, N. Y.  
Walker & Company, H. W., Chicago, Ill.  
Walker Vitamin Products, Inc., Mount Vernon, N. Y.  
Washington Institute of Medicine, Washington, D. C.  
White Laboratories, Inc., Newark, N. J.  
Williams & Wilkins Company, The, Baltimore, Md.  
Winthrop Chemical Company, Inc., New York, N. Y.  
Wyeth Incorporated, Philadelphia, Pa.  
Year Book Publishers, Inc., The, Chicago, Ill.

## OUTLINE OF CHICAGO SESSION

Hotel events are indicated in bold type

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	April 28	April 29	April 30	May 1	May 2
9:00 A.M. to 11:30 A.M.	Morning free. Registration, Exhibits, etc.	Hospital Clinics	Hospital Clinics	Hospital Clinics	Hospital Clinics
12:00 M. to 1:15 P.M.		Morning Lectures (9:30-11:30)	Morning Lectures (9:30-11:30)	Morning Lectures (9:30-11:30)	Morning Lectures (9:30-11:30)
1:15 P.M. to 2:00 P.M.		Panel Discussions	Panel Discussions	Panel Discussions	Panel Discussions
2:00 P.M. to 5:00 P.M.	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
5:00 P.M. to 8:00 P.M.	1st General Session	2nd General Session	3rd General Session	4th General Session Annual Business Meeting	5th General Session
	Dinner		Dinner		
8:00 P.M. to 11:00 P.M.	Entertainment and Opening Reception	Dinner	Convocation, followed by President's Reception	Annual Banquet	

**GENERAL SESSIONS PROGRAM****Ballroom, Palmer House**

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**FIRST GENERAL SESSION****Monday Afternoon, April 28, 1947****General Chairman, LeRoy H. Sloan, F.A.C.P., presiding****P.M.****2:15 Invocation.****His Eminence, Samuel Cardinal Stritch.****Addresses of Welcome.****The Mayor of the City of Chicago.****The Honorable DWIGHT GREEN, Governor of the State of Illinois.****MALCOLM T. MACFACHERN, F.A.C.P., President, Chicago Medical Society and Director of the American College of Surgeons.****JOSEPH L. BAER, F.A.C.S., President, Institute of Medicine of Chicago.****LAURENCE E. HINES, F.A.C.P., President, Chicago Society of Internal Medicine.****Response to Addresses of Welcome.****DAVID P. BARR, F.A.C.P., President of The American College of Physicians.****3:00 INTERMISSION.****President David P. Barr, F.A.C.P., presiding****3:20 Physical Diagnosis.****JAMES J. WARING, F.A.C.P., Professor of Medicine, University of Colorado School of Medicine, Denver, Colo.****3:40 The Role of Preventive Medicine in Clinical Practice.****WILSON G. SMILLIE (by invitation), Professor of Public Health and Preventive Medicine, Cornell University Medical College, New York, N. Y.****4:00 The Problem of the Neurotic Patient.****WILLIAM C. MENNINGER, F.A.C.P., Director, The Menninger Foundation; Consultant on Neuropsychiatry to the Surgeon General, U. S. Army; Member, Advisory Board to the Secretary of War; Topeka, Kans.****4:30 Life's Situations, Emotions, and Disease.****HAROLD G. WOLFF, F.A.C.P., Associate Professor of Medicine and Associate Professor of Psychiatry, Cornell University Medical College, New York, N. Y.****5:00 ADJOURNMENT.**

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**8:30 o'Clock****PROGRAM OF ENTERTAINMENT****Arranged by the Chicago Committee**

**SECOND GENERAL SESSION****Tuesday Afternoon, April 29, 1947****Presiding Officer****Hugh J. Morgan, F.A.C.P., Nashville, Tenn.****P.M.**

- 2:00 Streptomycin in the Treatment of Infections other than Tuberculosis.**  
**CHESTER S. KEEFER, F.A.C.P.,** Wade Professor of Medicine, Boston University School of Medicine, Boston, Mass.
- 2:20 Streptomycin in the Treatment of Tuberculosis.**  
**WALSH McDERMOTT** (by invitation), Associate Professor of Medicine, Cornell University Medical College; Assistant Attending Physician, The New York Hospital; New York, N. Y.
- 2:40 The Pharmacological Properties of Penicillin and their Bearing on Therapeutic Activity.**  
**HARRY EAGLE** (by invitation), Senior Surgeon, U. S. Public Health Service; Adjunct Professor of Bacteriology, Johns Hopkins University School of Hygiene; Director, Laboratory of Experimental Therapeutics, U. S. Public Health Service and Johns Hopkins University School of Hygiene; Baltimore, Md.
- 3:00 Treatment of Rickettsial Infections with Para-amino Benzoic Acid.**  
**JOHN C. SNYDER** (by invitation), Professor of Public Health Bacteriology, Harvard University School of Public Health, Boston, Mass.
- 3:20 INTERMISSION.**
- 3:40 Recent Advances in Malarial Chemotherapy.**  
**LOWELL T. COGGESHALL, F.A.C.P.,** Professor of Medicine and Chairman of the Department, University of Chicago School of Medicine, Chicago, Ill.
- 4:00 Mechanisms of Recovery in Bacterial Pneumonia.**  
**W. BARRY WOOD, JR., F.A.C.P.,** Professor of Medicine, Washington University School of Medicine; Physician-in-Chief, Barnes Hospital; St. Louis, Mo.
- 4:20 Tularemic Pneumonia.**  
**HUGH J. MORGAN, F.A.C.P.,** Professor of Medicine, Vanderbilt University School of Medicine; Consultant in Medicine to the Surgeon General, U. S. Army; Nashville, Tenn.
- 4:40 Primary Atypical Pneumonia.**  
**FRANK L. HORSFALL, JR.** (by invitation), Member, Rockefeller Institute of Medical Research; Physician, Hospital of the Rockefeller Institute; New York, N. Y.
- 5:00 ADJOURNMENT.**

**THIRD GENERAL SESSION****Wednesday Afternoon, April 30, 1947****Presiding Officer****James J. Waring, F.A.C.P., Denver, Colo.****P.M.**

- 2:00 Adrenal Cortical Syndromes and their Diagnoses.**  
**FULLER ALBRIGHT** (by invitation), John Phillips Medalist for 1947; Associate Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital; Boston, Mass.

- 2:40 **Use of Drugs in the Treatment of Diseases of the Muscles.**  
 ABNER McGEHEE HARVEY (by invitation), Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.
- 3:00 **INTERMISSION.**
- 3:20 **Effect of Shock on the Function of the Kidneys.**  
 DONALD D. VAN SLYKE (by invitation), Member, Rockefeller Institute of Medical Research, and in charge of study of metabolic diseases at the Hospital of the Rockefeller Institute, New York, N. Y.
- 3:40 **Humoral Factors of Hepatorenal Origin in Shock.**  
 EPHRAIM SHORR (by invitation), Associate Professor of Medicine, Cornell University Medical College; Attending Physician, The New York Hospital; New York, N. Y.
- 4:00 **Functional Pathology of Renal Disease.**  
 ARTHUR C. CORCORAN (by invitation), Member of Staff, Research Division, Cleveland Clinic Foundation, Cleveland, Ohio.
- 4:20 **Use of Tetraethyl Ammonium in Man in Evaluation of Vascular Tone.**  
 RICHARD H. LYONS, F.A.C.P., Associate Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.
- 4:40 **The Management of Hypertension.**  
 PAUL D. WHITE, F.A.C.P., Clinical Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital; Boston, Mass.
- 5:00 **ADJOURNMENT.**

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## ANNUAL CONVOCATION

Wednesday Evening, April 30, 1947

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8:30 o'Clock

Ballroom, Palmer House

T. Grier Miller, Marshal

All members of the profession and the general public are cordially invited. No admission tickets required.

Invocation.

The Right Reverend Wallace E. Conkling, S.T.D., D.D., Bishop of the Episcopal Diocese of Chicago.

1. The President's Address:

DAVID P. BARR.

2. Presentation of Newly Elected Fellows and Recital of the Pledge.

GEORGE MORRIS PIERSOL, Secretary General.

3. Presentation of the John Phillips Memorial Medal for 1947.

4. Announcement of Research Fellows for 1947-1948.

5. Convocational Oration: "Can UNESCO Succeed?"

GEORGE D. STODDARD, President,

University of Illinois, Urbana, Ill.; United States Delegate to the First General Conference of United Nations Educational, Scientific and Cultural Organization.



### President's Reception

The President's Reception and Dance will follow one-half hour after this program, in the Red Lacquer Room of the Palmer House. A cordial invitation is extended to all members and guests, with their families.

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## FOURTH GENERAL SESSION

Thursday Afternoon, May 1, 1947

P.M.

### 2:00 THE ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Reports will be received from the Secretary General, Executive Secretary and the Treasurer; elections of new Officers, Regents and Governors will take place; President-elect Hugh J. Morgan, of Nashville, Tenn., will be inducted as President and will make a brief inaugural address.

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Presiding Officer

A. B. Brower, F.A.C.P., Dayton, Ohio

### 2:45 Origin and Physiology of Heparin.

J. ERIK JORPES (by invitation), Associate Professor of Biochemistry, Caroline Institute, Stockholm, Sweden.

### 3:05 The Use of Dicoumarol as an Anticoagulant.

EDGAR V. ALLEN, F.A.C.P., Associate Professor of Medicine, Mayo Foundation; Chief of a Section, Division of Medicine, Mayo Clinic; Rochester, Minn.

### 3:20 A New Concept and Treatment of Purpura Hemorrhagica.

J. GARROTT ALLEN (by invitation), Chief Surgical Resident, Albert Merritt Billings Hospital, and Instructor in Surgery, University of Chicago School of Medicine, Chicago, Ill.

### 3:40 INTERMISSION.

### 4:00 The Current Status of Folic Acid.

CARL V. MOORE, JR., F.A.C.P., Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

### 4:15 Nitrogen Mustard in Treatment of Leukemia and Lymphoblastoma.

MAXWELL M. WINTROBE, F.A.C.P., Professor of Medicine and Head of the Department, University of Utah School of Medicine; Physician-in-Chief, Salt Lake County General Hospital; Salt Lake City, Utah.

### 4:30 Use of Radioactive Material in the Treatment of Blood Dyscrasias.

LEON JACOBSEN (by invitation), Assistant Professor of Medicine and Associate Dean, University of Chicago School of Medicine; Attending Physician, Albert Merritt Billings Hospital; Chicago, Ill.

### 4:45 Specific Diagnoses and Specific Therapy in Diseases Involving the Spleen.

CHARLES A. DOAN, F.A.C.P., Dean, Professor of Medicine and Director of Medical Research, Ohio State University College of Medicine, Columbus, Ohio.

**5:00 Chemotherapy of Multiple Myeloma.**

ISADORE SNAPPER (by invitation), Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons; Director, Postgraduate Medical Education, Mount Sinai Hospital; New York, N. Y.

**5:20 ADJOURNMENT.**

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**THE ANNUAL BANQUET OF THE COLLEGE**

Thursday Evening, May 1, 1947

8:00 o'Clock

Ballroom, Palmer House

(Procure tickets at the Registration Bureau)

Consult Special Banquet Program

Toastmaster: LeRoy H. Sloan, F.A.C.P., Chicago, Ill.

Address: Franklyn Bliss Snyder, President of Northwestern University

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**FIFTH GENERAL SESSION**

Friday Afternoon, May 2, 1947

Presiding Officer

Chauncey W. Dowden, F.A.C.P., Louisville, Ky.

P.M.

**2:00 Clinical and Pathological Comparison of Coronary Artery Disease in Different Age Groups.**

WALLACE M. YATER, F.A.C.P., Civilian Consultant, Army Institute of Pathology, Washington, D. C.

**2:20 Recent Advances in the Treatment of Cardiac Decompensation.**

EUGENE A. STEAD, JR., F.A.C.P., Professor of Medicine, Duke University School of Medicine, Durham, N. C.

**2:40 Convalescence, A Problem in Physiological Recovery.**

ROBERT W. KEETON, F.A.C.P., Professor of Medicine and Head of the Department, University of Illinois College of Medicine, Chicago, Ill.

**3:00 The Cardiac Lesions of Acute Disseminated Lupus Erythematosis.**

ELEANOR M. HUMPHREYS (by invitation), Associate Professor of Pathology, University of Chicago School of Medicine, Chicago, Ill.

**3:20 INTERMISSION.****3:40 The Management of Grand Mal and Petit Mal.**

FREDERIC A. GIBBS (by invitation), Associate Professor of Psychiatry, University of Illinois College of Medicine, Chicago, Ill.

**4:00 Human Factors in High Performance Aircraft.**

JAMES L. HOLLAND (by invitation), Captain, (MC), U.S.N., Flight Surgeon, Division of Aviation Medicine, Bureau of Medicine and Surgery, Navy Dept., Washington, D. C.

**4:20 Obesity: An Endocrine Problem.**

EDWARD H. RYNEARSON, F.A.C.P., Associate Professor of Medicine, Mayo Foundation; Consultant in Medicine, Mayo Clinic; Rochester, Minn.

**4:40 The Management of Saccular and Dissecting Aneurysm.**

LEROY H. SLOAN, F.A.C.P., Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill.

**5:00 ADJOURNMENT.**


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**MORNING LECTURES**

The Morning Lectures fulfill the increasing interest in fundamental problems and are planned to supplement the subject matter of the General Sessions. The Lectures, however, are organized to give the speaker adequate time to cover his presentation fully and to utilize charts, slides, motion pictures and other media to amplify his presentation.

The Lectures will be open to all members and guests of the College.

Admission by regular registration badge; no special tickets.

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**Tuesday, April 29, 1947**

**Ballroom, Palmer House**

**Presiding Officer**

William S. Middleton, F.A.C.P., Madison, Wis.

**A.M.**

**9:30-10:20 The Role of Amino Acids in Nutrition.**

WILLIAM C. ROSE (by invitation), Professor of Biochemistry, University of Illinois, Urbana, Ill.

**10:20-10:40 Intermission.****10:40-11:30 The Hormones of the Digestive Tract.**

ANDREW C. IVY, F.A.C.P., Distinguished Professor of Physiology and Vice President, University of Illinois, Chicago, Ill.

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**Wednesday, April 30, 1947**

**Ballroom, Palmer House**

**Presiding Officer**

T. Homer Coffen, F.A.C.P., Portland, Ore.

**A.M.**

**9:30-10:20 Hypersensitivity in the Pathogenesis of Collagen-Vascular Diseases.**

ARNOLD R. RICH (by invitation), Professor of Pathology, Johns Hopkins University School of Medicine, Baltimore, Md.

**10:20-10:40 Intermission.****10:40-11:30 The Pathogenesis of Lupus Erythematosus and Related Conditions.**

PAUL KLEMPERER (by invitation), Clinical Professor of Pathology, Columbia University College of Physicians and Surgeons; Pathologist, Mount Sinai Hospital; New York, N. Y.

Thursday, May 1, 1947

Ballroom, Palmer House

Presiding Officer

Walter B. Martin, F.A.C.P., Norfolk, Va.

A.M.

9:30-10:20 A Survey of Recent Developments Concerning the Concept of Coronary Disease and Its Management.

LOUIS N. KATZ, F.A.C.P., Director of Cardiovascular Research, Michael Reese Hospital, Chicago, Ill.

10:20-10:40 Intermission.

10:40-11:50 Newer Classifications and Interpretations of Hypertensive Diseases of the Retina.

PETER C. KRONFELD (by invitation), Associate Professor of Ophthalmology, University of Illinois College of Medicine; Acting Chief of Staff, Illinois Eye and Ear Infirmary; Chicago, Ill.

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Friday, May 2, 1947

Ballroom, Palmer House

Presiding Officer

T. Grier Miller, F.A.C.P., Philadelphia, Pa.

A.M.

9:30-10:20 Clinical Pathological Correlations of Infectious Hepatitis.

THOMAS N. HORAN, F.A.C.P., Physician, Harper Hospital, Detroit, Mich.

10:20-10:40 Intermission.

10:40-11:30 Infectious Hepatitis: Clinical Manifestations and Differential Diagnosis.

RICHARD B. CAPPS, F.A.C.P., Associate in Medicine, Northwestern University Medical School, Chicago, Ill.

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### PANEL DISCUSSIONS

The Panel Discussions for the 28th Annual Convention are concerned with topics of intimate interest and practical value to all members of the profession. Especially qualified men have been chosen as leaders and members of the panel personnel. These discussions will be held in the Palmer House from 12 noon to 1:15 P.M., Tuesday, Wednesday, Thursday and Friday.

Applications for tickets to Panel Discussions are to be made by members on the regular application forms accompanying the formal program. Tickets will also be available at the Registration Bureau in Convention Headquarters in the Palmer House.

Applicants may submit in writing any questions concerning any phase of the subjects in which they are especially interested. Such questions should be submitted to the General Chairman twenty-four hours before the Panel Discussion. Moderators and panel personnel will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions as time permits.

## PANEL DISCUSSIONS—Palmer House

Capacity	Red Lacquer Room 4th Floor 700	Crystal Room 3rd Floor 200	Room 14 Club Floor 250	Room 17 Club Floor 200	Room 18 Club Floor 125
Tuesday April 29 12:00 M. to 1:15 P.M.	<b>I</b> <b>Electrocardiography</b> Moderator *Louis N. Katz, Chicago Emmet B. Bay, Chicago *Roy W. Scott, Cleveland *Frederick A. Willius, Rochester, Minn. *Frank N. Wilson, Ann Arbor	<b>II</b> <b>Chemotherapy</b> Moderator *Hugh J. Morgan, Nashville Harry Eagle, Baltimore *Chester S. Keefer, Boston Walsh McDermott, New York Irwin Peters, Chicago *Wesley W. Spink, Minneapolis *W. Barry Wood, Jr., St. Louis	<b>III</b> <b>Newer Aspects of the Treatment of Peptic Ulcer</b> Moderator *Walter L. Palmer, Chicago *Walter C. Alvarez, Rochester, Minn. *Philip W. Brown, Rochester, Minn. *Lester R. Dragstedt, Chicago *Sara M. Jordan, Boston Waltman Walters, Rochester, Minn.	<b>IV</b> <b>Diseases of the Liver</b> Moderator Frank C. Mann, Rochester, Minn. *M. Herbert Barker, Chicago *Hugh R. Butt, Rochester, Minn. *James F. Weir, Rochester, Minn. *Guy W. Wells, Providence	<b>V</b> <b>Renal Diseases</b> Moderator *Harold C. Lueth, Omaha Norris J. Heckel, Chicago *Laurence E. Hines, Chicago *Francis D. Murphy, Milwaukee Reed M. Nesbit, Ann Arbor
Wednesday April 30 12:00 M. to 1:15 P.M.	<b>VI</b> <b>Medical Aspects of Cardiovascular Surgery</b> Moderator *Paul D. White, Boston Max Minor Peet, Ann Arbor Willis J. Potts, Chicago *William D. Stroud, Philadelphia	<b>VII</b> <b>Psychosomatic Medicine</b> Moderator *William C. Menninger, Topeka Franz G. Alexander, Chicago *Henry W. Brosin, Chicago Hugh T. Carmichael, Chicago Roy R. Grinker, Chicago *Sidney A. Portis, Chicago David Slight, Chicago	<b>VIII</b> <b>Endocrinology, Including Diseases of the Thyroid</b> Moderator *Willard O. Thompson, Chicago Willard M. Allen, St. Louis Edwin B. Astwood, Boston *Elmer C. Bartels, Boston *Samuel F. Haines, Rochester, Minn. *Edward H. Ryneerson, Rochester, Minn. Ephraim Short, New York Mayo H. Soley, San Francisco	<b>IX</b> <b>Myopathies</b> Moderator *Andrew C. Ivy, Chicago Eben J. Carey, Milwaukee Herman Chor, Chicago Abner McG. Harvey, Baltimore	<b>X</b> <b>Allergy</b> Moderator *Harry L. Huber, Chicago *Samuel M. Feinberg, Chicago *Richard A. Kern, Philadelphia *Louis E. Prickman, Rochester, Minn.

## PANEL DISCUSSIONS—Palmer House—Continued

Capacity	Red Lacquer Room 4th Floor	Crystal Room 3rd Floor	Room 14 Club Floor	Room 17 Club Floor	Room 18 Club Floor
Thurs May 1 12:00 M. to 1:15 P.M.	700 XI Hematology Moderator *William B. Castle, Boston  *Israel Davidsohn, Chicago *Charles A. Doan, Columbus, Ohio J. Erik Jorpes, Stockholm, Sweden *Carl V. Moore, St. Louis Edward H. Reinhard, St. Louis Isadore Snapper, New York *Maxwell M. Wintrobe, Salt Lake City	200 XII Tumors of the Mediastinum Moderator Jerome R. Head, Chicago  Paul C. Hodges, Chicago Cecil A. Krakower, Chicago T. C. Laipply, Chicago Daneley P. Slaughter, Chicago Willard Van Hazel, Chicago	250 XIII Peripheral Vascular Disease—Anticoagulant Therapy Moderator *Edgar V. Allen, Rochester, Minn.  *Walter F. Kvale, Rochester, Minn. Karl Paul Link, Madison *Gilbert H. Marquardt, Chicago *Ovid O. Meyer, Madison Geza de Takats, Chicago *Theodore R. Van Dellen, Chicago	200 XIV Headache Moderator *Harold G. Wolff, New York  *Bayard T. Horton, Rochester, Minn. Eric Oldberg, Chicago Lewis J. Pollock, Chicago	125 XV Polomyelitis Moderator Hart E. Van Riper, New York  Edward Piczak, Chicago Arthur Steindler, Iowa City Philip M. Stimson, New York Maurice B. Visscher, Minneapolis James L. Wilson, Ann Arbor
Friday May 2 12:00 M. to 1:15 P.M.	XVI Cardiology Moderator *James E. Paulin, Atlanta  *Newell C. Gilbert, Chicago *William J. Kerr, San Francisco *Jonathan C. Meakins, Montreal *William D. Stroud, Philadelphia *J. Edwin Wood, Jr., Charlottesville *Wallace M. Yater, Washington, D. C.	XVII Respiratory Diseases Moderator *Francis G. Blake, New Haven  *Robert G. Bloch, Chicago *Robert O. Brown, Santa Fe *Francis M. Pottenger, Sr., Monrovia *Paul S. Rhoads, Chicago	XVIII Rheumatic Diseases Moderator *Russell L. Cecil, New York  *Hugo A. Freund, Detroit *Richard H. Freyberg, New York *Philip S. Hench, Rochester, Minn. *W. Paul Holbrook, Tucson *Ralph A. Kinsella, St. Louis	XIX Edema Moderator *Eugene A. Stead, Jr., Durham  Norman M. Keith, Rochester, Minn. Louis Leiter, New York *Ferdinand R. Schemm, Great Falls	XX Nutritional Disorders Moderator *John B. Youmans, Chicago  Paul R. Cannon, Chicago *Anton J. Carlson, Chicago *Robert W. Keeton, Chicago *Tom D. Spies, Birmingham

Somerville; Morristown Memorial Hospital; Newton Memorial Hospital; and Monmouth Memorial Hospital, Long Branch.

His society affiliations were the following: Morris County Medical Society (President 1907); Essex County Medical Society; Judicial Council of the N. J. State Medical Society 1912-46; Charter Member Academy of Medicine of Northern N. J.; New York Academy of Medicine; New York Neurological Society; first president of the New Jersey Neuro-psychiatric Association; British Medical Association; American Medical Association; American Neurological Association; American Psychiatric Association; Association for Research in Nervous and Mental Diseases; American College of Physicians (F.A.C.P., 1917). He was a Trustee of the Society for Relief of Widows and Orphans of Medical Men of New Jersey.

He contributed various articles to medical publications and was an active attendant at medical meetings. His influence was wide throughout the State and his absence will be keenly felt in many quarters. Golf, tennis, fishing, and landscape painting were his pastimes and hobbies.

He is survived by his wife, Lucille Abbott Beling; a son, Dr. Christopher Abbott Beling, whose chief interest is in neuro-surgery; and a daughter, Mrs. James A. Richardson.

GEORGE H. LATHROPE, M.D., F.A.C.P.,  
Governor for N. J.

### DR. EMMANUEL PERSILLIER BENOIT

Dr. Emmanuel P. Benoit, F.A.C.P., died on April 14, 1946, at his home in Montreal, aged 77 years.

Born in 1869 he qualified for his M.D. degree in 1892, and four years later became attached to the Medical Clinic of Notre Dame Hospital of which he was named chief clinician in 1908. With this Institution he was affiliated for almost half a century until his retirement in 1940.

In 1899 he succeeded to the chair of Internal Pathology at Laval University, and in 1913 was made a member of the Council of the Medical Faculty of which he was Secretary from 1929 to 1945.

In addition to the above Dr. Benoit devoted much time and energy to the organization of the nursing profession, both male and female, and their affiliation with the medical faculty.

He was Officer of the Academy, corresponding Member of the Academy of Medicine of Paris, and was one of the early Fellows of the American College of Physicians. He was also honorary member of the Medical Society of Montreal, President of the Commission of Nurses, Director of the Medical Service of the Sauvegarde Assurance Company, and Editor-in-chief of the Union Medicale from 1897-1900, and on the Editorial Staff until his death.

A skilled physician, possessed of extraordinary diagnostic acumen and wide learning, he was known also for his simplicity and modesty; his in-

tellectual vigour and integrity and withal, his ever questing spirit which his magnificent library served to gratify and at the same time to stimulate.

He leaves a wife and three sons.

A. T. HENDERSON, M.D., F.A.C.P.,  
Governor for Quebec

### DR. JAMES MURRAY FLYNN

Dr. James Murray Flynn, M.D., F.A.C.P., Rochester, N. Y. Born at Rochester, March 29, 1883; M.D., 1914, University of Buffalo School of Medicine; Interne, 1913-14, Buffalo General Hospital; Interne also at the Moses Taylor Hospital at Lackawanna, N. Y., and the Rochester General Hospital between 1914 and 1916; postgraduate courses in radiology taken at Cornell University and at Cook County Hospital, Chicago; practice limited to radiology since 1917; Diplomate, American Board of Radiology; served in World War I; Radiologist for many years at Rochester General Hospital, St. Mary's Hospital, Park Avenue Hospital; Consulting Radiologist, Monroe County Infirmary; Consultant in Radiology, School of Medicine and Dentistry, Strong Memorial Hospital, University of Rochester; served as former president of the Monroe County Medical Society, Rochester Academy of Medicine, Rochester Pathological Society, Seventh District Branch of the Medical Society of the State of New York, and of the Medical Society of the State of New York; Fellow and Member of the House of Delegates of the American Medical Association; Member, Radiological Society of North America and American Roentgen Ray Society; Fellow of the American College of Radiology and of the American College of Physicians, the latter since 1939; author of numerous published papers; died December 14, 1946, at the age of 63, of coronary disease and pneumonia.

Dr. Flynn was very highly respected by the members of his profession. His death is a distinct loss to the citizens and profession of Rochester, N. Y.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,  
Governor for Western New York

### DR. GEORGE BERNARD TOPMOELLER

Dr. George Bernard Topmoeller, M.D., F.A.C.P., age 59, died October 3, 1946, at Good Samaritan Hospital in Cincinnati, after a brief illness, of gastric ulcer with recent hemorrhages. He was born in Cincinnati, Ohio, May 19, 1887. He received his early education at St. Augustine School and St. Xavier High School. Later he attended St. Xavier College. In 1910 he received his M.D. degree from the Medical College of The University of Cincinnati and entered upon a year of internship at the Good Samaritan Hospital.

Dr. Topmoeller accepted his professional responsibilities with great earnestness and conscientiousness. Never wishing to fall behind in the procession of medical progress he availed himself, at frequent intervals, of



intensive postgraduate work. In 1929 he worked in gastro-enterology at Harvard University Medical College and in 1930 in Germany. In 1936 he was elected to fellowship in the American College of Physicians and in 1937 he was made a Diplomate of the American Board of Internal Medicine. He became Chief of Staff of both Good Samaritan Hospital and St. Mary's Hospital.

In World War I he was commissioned First Lieutenant and was stationed at Camp Lee, Virginia. In World War II he devoted one day a week to the examination of recruits and served on the Board of the Procurement and Assignment Commission. He was appointed Senior Surgeon in the Reserve of the United States Public Health Service.

To quote the Cincinnati Journal of Medicine, December, 1946—"In the death of Dr. George Bernard Topmoeller we realize that our city has lost a man of exemplary character and a highly esteemed and skilled physician; that the medical profession has lost a worthy colleague who has ever been fair in all his dealings with his fellow physicians; and that the Cincinnati Academy of Medicine has lost a valuable member who was always willing to serve it to the fullest of his ability."

M. A. BLANKENHORN, M.D., F.A.C.P.,  
Governor for Ohio

#### DR. JAMES R. E. BARNES

Dr. James R. E. Barnes (Associate), Cicero, Ill., died June 16, 1946.

He was born in 1877 and received his medical training at the Jenner Medical College, 1904.

Dr. Barnes became an Associate of the College by virtue of membership in the old American Congress on Internal Medicine, having been a charter member of that organization from 1915. When the Congress was merged with the College in 1926, Dr. Barnes became an Associate.

His death was due to cerebral hemorrhage and diabetes mellitus.

#### DR. ERLE BULLA CRAVEN, JR.

Dr. Erle Bulla Craven, Jr., Lexington, N. C., died June 19, 1946, following an illness of two years' duration.

Dr. Craven was born at Lexington, N. C., September 9, 1905. He held an A.B. degree from Duke University and an M.D. degree from Johns Hopkins University School of Medicine. He was an interne at Johns Hopkins Hospital and a Resident in Pathology at Duke University Hospital. Before his illness he was an Associate in Medicine, Duke University School of Medicine; Director of Laboratory, Davidson Hospital; a member of the Davidson County Medical Society, North Carolina Medical Society, and a Fellow of the American Medical Association. He had been a Fellow of The American College of Physicians since 1939, and was a Diplomate of the American Board of Internal Medicine.

# ANNALS OF INTERNAL MEDICINE

VOLUME 26

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NUMBER 3

## THE SEPARATION OF BLOOD INTO FRACTIONS OF THERAPEUTIC VALUE \*

By EDWIN J. COHN, *Boston, Massachusetts*

### I. INTRODUCTION

Medicine is concerned with understanding, in the interests of control, all of the component parts of the body and their functioning. Anatomy and physiology have contributed to this understanding, as have histology, bacteriology and immunology. Alchemy has contributed both to pharmacology and to chemistry, and an unfolding chemistry has contributed a knowledge

\* John Phillips Memorial Medalist Presentation to the Twenty-Seventh Annual Session of the American College of Physicians, Philadelphia, Pennsylvania, May 14, 1946.

This work was originally supported by grants from the Rockefeller Foundation and from funds of Harvard University. It was aided early in 1941 by grants from the Committee on Medicine of the National Research Council, which included a grant from the American College of Physicians. Since August, 1941, it has been carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

This paper is Number 51 in the series "Studies on Plasma Proteins" from the Harvard Medical School, Boston, Massachusetts, on products developed by the Department of Physical Chemistry from blood collected by the American Red Cross.

Our knowledge of blood has been accumulating for so many centuries that adequate references to the literature regarding each point referred to would occupy more space than this brief essay. The quotation from Mayow is from the article by T. S. Patterson, *Isis*, 1931, xv, 504. The quotation from Mulder is from page 101, and that from Liebig is from pages 38 and 39 of Liebig, J., *Animal Chemistry, or Organic Chemistry in Its Application to Physiology and Pathology*, John Owen, Cambridge, 1843. References to Mulder's early estimates of protein molecular weights and to the communication from Denis to Liebig are given in a paper on Proteins as Chemical Substances and as Biological Components in the *Bulletin of the New York Academy of Medicine*, 1939, xv, 639. A partial bibliography regarding blood and blood derivatives is published in *Science in Progress*, Yale University Press, Fourth Series, pages 319-23, 1945. Earlier chemical methods for the separation and purification of the plasma proteins were considered in *Chemical Reviews*, 1941, xxviii, 395, and the newer methods of plasma fractionation in ethanol-water mixtures of controlled pH, ionic strength and temperature were reported in the *Journal of the American Chemical Society*, 1940, lxii, 3396, and 1946, lxviii, 459. Recent studies upon separated plasma components which have led to clinical uses have been reported in the *Journal of Clinical Investigation*, 1944, xxiii, 417-606; 1945, xxiv, 657, 662, 671, 698, 704, 793, 802, and 1946, xxv, 304; and articles to be published shortly in the same journal; in the *Journal of the American Medical Association*, 1944, cxxiv, 976; 1944, cxxvi, 469, 674, 680, 944; 1945, cxxvii, 144; 1945, cxxviii, 1062, 1088; and 1945, cxxix, 270; in the *Bulletin of the New York Academy of Medicine*, Second Series, 1945, xxi, 202; in *Surgery*, 1945, xviii, 347; and in the *American Journal of the Medical Sciences*, 1945, ccx, 661.

first of the elements, then of their relation to each other in the organic molecule and then of intermolecular reactions. The level of understanding, at any time, has reflected the new knowledge in the natural, as well as in the medical sciences.

*Discovery of the Atmospheric Gases.* The chemistry of the sixteenth and seventeenth centuries related to the blood largely through the concern of Boyle, Hooke, and Newton with the nature of the elements, especially the gases of the atmosphere. The need of air for life was recognized. Hooke noted that the movement of the lungs was merely a mechanical device for bringing air into the body and proved by experiment that an animal could be kept alive without any movement of the lungs, provided air was driven in, by a bellows, and permitted to escape by mechanical means. These brilliant early experiments in artificial respiration were supplemented by the observations of his contemporary, Mayow, "that animals exhaust the air of certain vital particles, . . . that some constituent of the air absolutely necessary to life enters the blood in the act of breathing." The vital constituent was, of course, oxygen. Mayow had thus noted the rôle in respiration of the oxygen in the air, Hooke the rôle of the lungs, Harvey of the heart, Malpighi of the capillaries, and Leeuwenhoek had noted the red blood corpuscles in the blood stream. The anatomical and physical advances in Italy and in England had by 1700 thus made possible some understanding of the mechanical bases of respiratory processes.

*Development of Organic Chemistry.* The observations of these natural philosophers had been appraised and organized into a system of quantitative knowledge by Lavoisier in the eighteenth century and again expanded in an exploration of the more complex organic molecules of natural systems, by Liebig and Berzelius, during the first part of the nineteenth century. The new tools that were becoming available led to Wöhler's synthesis of urea in 1828. More than a century later, although these tools had been successfully employed by Emil Fischer and his school in the synthesis of peptides from amino acids, the synthesis of the larger and more complex protein molecules, though composed of amino acids bound in peptide linkage, had not been accomplished. Meanwhile, synthetic organic chemistry had created a revolution which temporarily distracted attention from the natural products and systems of which the body is composed. The use of these tools in the exploration of the by-products of coal tar distillation and in the synthesis of simple organic molecules by Hofmann, Perkin, Baeyer, and Ehrlich preoccupied men's minds. The tradition of Paracelsus was reborn with the development of the pharmacology of unnatural products; of aspirin, phenacetin and salvarsan and, in our time, of the sulfa drugs and DDT.

*Development of Descriptive Protein Chemistry.* These brilliant achievements led to the temporary eclipse of observations on the natural substances of the body. The first of the amino acids to be discovered was the cystine of cystine stones described by Wollaston in 1810. Cystine was, however, not recognized as a constituent of proteins until eighty years later. Until

1865 but three amino acids had been isolated from proteins; leucine by Proust in 1819, glycine by Braconnot in 1820 and tyrosine by Liebig in 1846. Liebig had become professor of chemistry at Giessen in 1826 and the medical faculty honored him with its doctorate. A great school of protein chemists had its focus in Liebig's laboratory. In 1837 he published an "Introduction to the Analysis of Organic Bodies." Estimates were made of the great size of proteins based upon their elementary composition by Mulder, who first gave the name "protein,"—from the Greek meaning "I take the first rank"—to what he "considered as the commencement and starting-point of all other animal tissues, because these are all produced from the blood."

The British Association in 1840 acclaimed Liebig's report on "Chemistry in Its Application to Agriculture and Physiology," which was amplified in a second report to the Association in 1842, translated and published as "Animal Chemistry or Organic Chemistry in Its Application to Physiology and Pathology" by his enthusiastic contemporaries, William Gregory of King's College, Aberdeen, and John Webster of Harvard. In it Liebig wrote:

"Two substances require especial consideration as the chief ingredients of the blood; one of these separates immediately from the blood when withdrawn from the circulation. It is well known that in this case blood coagulates, and separates into a yellowish liquid, the *serum* of the blood, and a gelatinous mass, which adheres to a rod or stick, in soft, elastic fibres, when coagulating blood is briskly stirred. This is the *fibrine* of the blood, which is identical in all its properties with muscular fibre, when the latter is purified from all foreign matters.

"The second principal ingredient of the blood is contained in the serum, and gives to this liquid all the properties of the white of eggs, with which it is identical. When heated, it coagulates into a white elastic mass, and the coagulating substance is called *albumen*.

"Fibrine and albumen, the chief ingredients of blood, contain, in all, seven chemical elements, among which nitrogen, phosphorus, and sulphur are found. They contain also the earth of bones. The serum retains in solution sea salt and other salts of potash and soda, in which the acids are carbonic, phosphoric, and sulphuric acids. The globules of the blood contain fibrine and albumen, along with a red coloring matter, in which iron is a constant element. Besides these, the blood contains certain fatty bodies in small quantity, which differ from ordinary fats in several of their properties."

During this time Bence-Jones carried out studies on proteins in part with Liebig, and the French physician, Denis, communicated to Liebig his observations upon blood proteins, which we now call globulins, which are soluble in neutral salt solutions; observations which he later extended and presented to the Académie des Sciences as a "Mémoire sur le Sang Considéré quand il est Fluide, pendant qu'il se Coagule et lorsqu'il est Coagulé."

*Development of Physical Chemistry.* The attack on the chemistry of the proteins was not resumed with equal vigor and talent until late in the nineteenth century. Knowledge of the laws governing natural systems developed more rapidly than knowledge of the nature of the substances. Poiseuille, a French physician, deduced the laws of viscous flow because of his

interest in the capillaries of the body. Pfeffer and de Vries, two botanists, laid the foundations for our understanding of osmotic pressure as a result of their interest in the forces governing the movement of water in trees and in cells. These observations led to the concept of isotonicity and were extended by Hedin and Hamburger to the passage of water into and out of the red blood cell. All of these observations played an important rôle in the development of physical chemistry which—starting in 1878 when Van't Hoff applied the gas laws to solutions and Arrhenius, in the following year, explained the discrepant behavior of salts as due to their electrolytic dissociation into ions—has made possible understanding, first of the behavior in aqueous solution of inorganic ions and, finally, of even such complex organic ions as the proteins.

*Development of Protein Physical Chemistry.* Although Claude Bernard, Hoppe-Seyler and Hofmeister, among others, were concerned with the behavior of proteins and contributed technics for their preparation, the foundations for the present rich development, both in the theory and the practice of protein chemistry, were largely laid by Sir William Hardy at the turn of this century. In 1899 he supplemented earlier observations and correctly interpreted the movement of proteins in an electric field as due to their dissociation as electrolytes. Moreover, he demonstrated that their electrophoretic mobilities could vary, not only in amount but also in direction; thus demonstrating that proteins were amphoteric electrolytes.

If proteins were electrolytes it followed that protein ions were in equilibrium with the other ions of the body. If proteins were amphoteric electrolytes it followed that, though they bore positive electric charges in acid solution and negative electric charges in neutral and alkaline solutions, there would be a zone in which they bore no excess of positive or of negative charges and thus were in an isoelectric condition. Improvements in methods of characterizing proteins in terms of their electrophoretic mobilities and isoelectric points have since been made by Pauli and Michaelis, by Sørensen and Tiselius. Enzymes and hormones as well as the proteins of the blood and other tissues have been considered in these terms. Most of the proteins have been found isoelectric between pH 4.5 and 7.5 and to be far less soluble in the neutral isoelectric than in the ionic condition.

Hardy's observations extended to the interactions of isoelectric proteins and salts. In 1905 two great papers were published in the *British Journal of Physiology* on the serum proteins: the one by Hardy, the other by Mellanby. The interaction of proteins with salts was critically examined and the more than half century old observations of Denis on the class of serum proteins, the globulins, that are soluble in salt solutions but not in water, quantitatively formulated in terms of the concentration and the valence of the salt ions.

The further interpretation of this phenomenon had to await two advances in physical chemistry, both contributed in 1923. In that year Bjerrum offered evidence for the view that amino acids and therefore proteins, in-

stead of being uncharged molecules in the neutral condition as had previously been assumed, were dipolar ions; that is, they bore equal numbers of positive and negative charges.

There was no satisfactory approach that could be applied to our understanding of solutions of ions, dipolar ions and uncharged molecules until in 1923 Debye developed the electrochemical theory of solutions which accounts for the interaction of ions with each other as well as with organic molecules. In terms of electrostatic forces, the solvent action of salts upon globulins depends not only upon the number of electrical charges on the protein, but also upon their spatial distribution on its surface. If all of the positive and negative electric charges, which result from the amphoteric dissociation of proteins, respectively as acids and bases, are distributed symmetrically, a positive charge being surrounded by negative charges, and a negative charge being surrounded by positive charges, the interaction with inorganic ions is small. If, however, there is less electrical symmetry, so that on the average there is a larger concentration of positive electric charges at one side of the molecule and of negative electric charges at the other, the molecule has an electric moment. Though a neutral molecule cannot migrate in the electric field it orients in it, thereby increasing the dielectric constant of the solution. The interaction of proteins and electrolytes, which results in the phenomenon of the solubility of globulins in neutral salt solutions, is a function of the concentration and valence of the salt and of the electric moment of the protein.

Globulins are not the only proteins which interact with electrolytes in this way. Albumins do also. Albumins, however, are so soluble in water that their interactions with salts are observed only by measurements other than solubility or in other environments. The methods of purifying and crystallizing albumins in concentrated salt solutions, introduced in the last century by Hoppe-Seyler and Hofmeister, and perfected in this century by Sir Frederick Gowland Hopkins and S. P. L. Sørensen, obscure these relations by superimposing the non-specific mass effects of "salting-out" which apply to gases, organic molecules and other electrolytes, as well as to proteins.

Proteins may be precipitated not only by "salting-out" but also by the addition of alcohols, acetone or other water-miscible organic solvents to their solutions. Such additions at ordinary temperatures generally lead to protein denaturation. Irreversible changes in the labile protein molecule can generally be minimized, however, if the temperature is maintained sufficiently low. Sir William Hardy had observed this phenomenon during the first world war, in which his attention had been directed to the conditions for the preservation of food. Temperatures of  $0^{\circ}\text{C}$ . do not suffice, but temperatures below zero, but above the freezing point of the solution, are readily achieved in alcohol- or acetone-water mixtures. In order to investigate the interactions of albumin and neutral salts, under conditions in which the solubility of the protein was low, advantage was taken of this observation. The solubility of egg albumin was studied in 25 per cent ethanol at  $-5^{\circ}\text{C}$ .

beginning in 1932 in collaboration with my colleague, R. M. Ferry. Under these conditions denaturation was minimized. Indeed, the egg albumin, a readily denatured protein, could be recrystallized after being in 25 per cent ethanol at  $-5^{\circ}$  C. for a month if the ethanol was removed before the temperature was raised. More important from a theoretical point of view, neutral salts increased the solubility of the albumin under these conditions much as they do the solubility of globulins in water.

## II. SOLUBILITY OF PROTEINS IN ALCOHOL-WATER MIXTURES OF CONTROLLED pH, IONIC STRENGTH AND TEMPERATURE

This investigation of the interaction of proteins and salts in ethanol-water mixtures at sub zero temperatures—undertaken to supplement comparable studies on amino acids and peptides of known structure, varying in electric moment and non-polar groups and thus in solubility—laid the foundation for the separations of plasma proteins that have been carried forward during this war.

*The Use of Alcohol as a Protein Precipitant* made possible protein fractionations at the low salt concentrations at which protein-salt interactions are maximum. This theoretical advantage has proved of great practical value in making possible the separation of proteins of closely related properties. Moreover, the small amount of salt separating with the protein precipitate rendered unnecessary the long dialysis, required to remove the large amount of salt from proteins prepared by "salting-out," before they could be injected into the body. The new conditions of fractionation in alcohol-water mixtures at low temperatures are essentially bacteriostatic. By reducing bacterial growth they have reduced the accompanying danger of pyrogenic reactions.

*The Choice of a pH*, close to the isoelectric point of the protein to be precipitated, and therefore close to its minimum solubility, rendered unnecessary the use of high concentrations of alcohol. Thus, 25 per cent ethanol sufficed for the precipitation of globulins of neutral isoelectric points at neutral pH, and 40 per cent ethanol for the more acid globulins and albumins at pH zones near their isoelectric points.

*The Temperature* was maintained close to the freezing point of the alcohol-water mixture at alcohol concentration less than 15 volumes per cent. At that and higher alcohol concentrations temperatures of  $-5^{\circ}$  C. or  $-10^{\circ}$  C. were chosen depending upon the lability and the heat of solution of the protein to be separated.

*The Ionic Strength* was reduced to any desired point following the initial precipitation of a protein fraction. Since euglobulins by definition are insoluble in water in the absence of salt, they separated readily at sufficiently low ionic strength, at the appropriate pH, following an initial precipitation from an alcohol-water mixture at low temperature.

*Lipoproteins* of different molecular size, physical and chemical characteristics and isoelectric points, and containing respectively 35 and 75 per

cent lipid, have been prepared in this way and the nature of their interactions with salt, and of the interactions holding and transporting lipid in combination with protein in aqueous solution in the blood stream, investigated.

*Among Proteins with the Same Isoelectric Points* differences in the influence of salt on their solubility, even at the same alcohol content and temperature, is a most effective method of achieving their separation. Specific interactions with ions which either have solvent or precipitating actions, other than those due to their ionic strength, have proved useful within the framework of this multivariable system. In the fractionation of plasma proteins that has been carried out for the Armed Forces on a large scale with the blood of roughly two and one-half million donors to the American Red Cross, a five-variable system has sufficed in which the limits were as follows:

Variable	Limits Employed		
pH	4.4	to	7.4
$\Gamma/2$	0.001	to	0.16
Ethanol concn., mole fraction	0	to	0.163
Ethanol concn., vol. % at 25°	0	to	40
Protein concn., g./liter	0.2	to	66
Temperature, °C.	0	to	-10

These conditions have been attained, and the variables maintained constant, by the use of acetate and carbonate buffer systems to control pH and ionic strength, and by the use of ethanol as precipitant since it was readily removed by distillation. These reagents are both convenient for the processing of biological systems and safe to use in the preparation of protein and lipid products, even where large quantities are destined for intravenous use.

### III. THE SEPARATION OF PLASMA INTO FRACTIONS

Although the methods that have been developed for protein and lipoprotein fractionation are general in nature and applicable to any biological tissue, we shall, in this presentation, limit consideration to human blood. The microscope revealed, and the centrifuge facilitated, the separation of the cellular elements of the blood from the plasma. Differences in density further permit separation of the red cells from the white cells. The gross separations of the various cellular elements and the plasma is thus the first step in the dissection, first by mechanical, and then by chemical means, of this complex tissue.

*The Red Blood Cells* contain the respiratory protein, hemoglobin. The oxygen-combining capacity of the red cell has been treated often and completely by Barcroft, Haldane, Henderson and later workers. The complex system which is the red blood cell contains not only hemoglobin but also a large number of protein enzymes, including phosphatase, hypertensinase, cholinesterase, catalase and carbonic anhydrase. Although satisfactory evidence is not available of the value in therapy of these proteins, when separated from the cell in which they are concentrated in nature, the study of each of them should, at the least, yield further knowledge of their chemistry, their interactions and their functions.



*The White Cells* have been studied from the point of view of histology and bacteriology. The chemistry of their components, however, remains largely to be investigated. One enzyme, veridoperoxidase, has been shown by Agner to be present to about 1 per cent. The relation of the white cells to thromboplastic activity and to hemophilia has been suggested, but definitive chemical products concerned with these and other functions have thus far not been isolated.

*The Plasma*, according to Liebig, contained fibrinogen and albumin. Denis noted the salt-soluble globulins. The efforts to separate globulins further by means of this phenomenon or by "salting-out," attempted by many

### RELATIVE DIMENSIONS OF VARIOUS PROTEINS

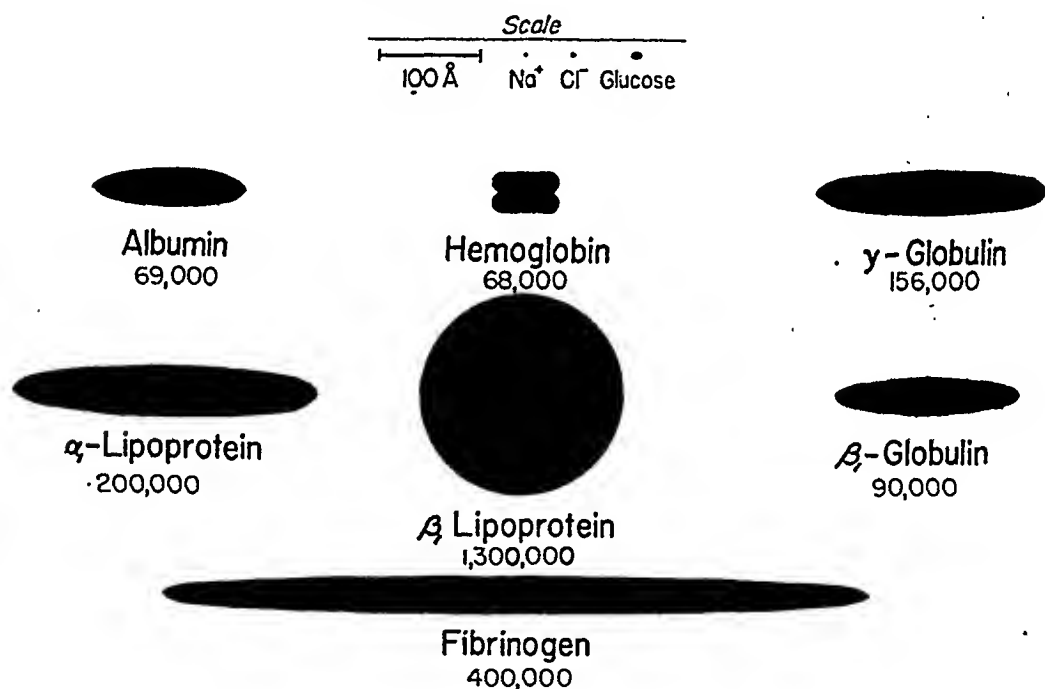


FIG. 1.

\* Revised by J. L. Oncley from Figure 1, in COHN, E. J.: Blood and blood derivatives, Am. Scientist, 1945, xxxiii, 66.

and most critically by Sørensen, has not yielded chemical individuals. The characterization of globulins in terms of their molecular size was made possible by the ultracentrifuge developed by Svedberg. Studies in Sweden, in England, and in various laboratories in the United States carried out by means of the ultracentrifuge and other physical chemical methods, especially diffusion, viscosity and double refraction of flow, have revealed proteins of the same diameter and twice the length of albumin; still longer globulins and spherical euglobulins. All are larger than the albumins and less asymmetric than fibrinogen (figure 1).

The study of globulins in terms of their electrophoretic mobility in neutral or alkaline solution has led to the classification, due to Tiselius, of α-, β- or

$\gamma$ -globulins. More recent observations have revealed in each class proteins moving with somewhat different mobilities which have been designated as  $\alpha_1$ - and  $\alpha_2$ -,  $\beta_1$ - and  $\beta_2$ -globulins. This classification, though useful, is also inadequate for the characterization of the diverse components of the plasma, the concentration of each of which may well be essential in maintaining a specific bodily function. Even at the present state of knowledge we recognize, in terms of other chemical or physical chemical properties, several  $\alpha_1$ -globulins and at least four  $\beta_1$ -globulins.

Recognizing the very large number of components of which plasma is constituted, the chemical method for its fractionation was devised in such a way as to take advantage of differences in solubility which reflected differences in molecular size and electric charge, in non-polar side chains or in dissociated polar groups leading to different isoelectric points and electric moments. In the interest of large scale processing, plasma was first separated into as few major fractions as possible. Each fraction precipitated was then subjected to subfractionation under the conditions found most effective for the further separation and isolation of chemical components. The process that has been developed during this war, modified from time to time so as to effect the separation of all protein and lipoprotein components in as nearly their natural states as possible, yields six major fractions.

*Fraction I* contains most of the fibrinogen and the antihemophilic globulin.

*Fraction II*, obtained by subfractionation of II + III, contains the  $\gamma$ -globulin antibodies of proven value in the prophylaxis of measles and probably also of infectious hepatitis.

*Fraction III-1* contains other antibodies, including those to typhoid 0.\* The isoagglutinins, including the anti-Rh antibodies of value in blood typing, are also concentrated in this fraction.

*Fraction III-2* contains prothrombin and one of the components of complement. Prothrombin converted by thromboplastin to thrombin has proved of value in conjunction with fibrin foam or some other pledget as an hemostatic agent and, in conjunction with fibrinogen, in the formation of clots, films as dural substitutes and tubes for other surgical uses.

*Fraction III-3* contains plasminogen, the precursor of plasmin, which has sometimes been called the fibrinolytic enzyme.

*Fraction III-0* is rich in lipoprotein, including the so-called X-protein of McFarlane, which interacts in the plasma in such a way as to suggest that its molecular weight varies with concentration. The lipoproteins in this, and the next fraction listed are the bearers of cholesterol and carotene and of such steroids as estriol and vitamin A.

*Fraction IV-1* is lipoprotein in nature. From the point of view of electrophoresis the lipoprotein in IV-1 is  $\alpha_1$ -globulin, that in Fraction III-0,  $\beta_1$ -globulin. From the point of view of size (see figure 1), that in Fraction

\* In animals many antitoxins occur in this fraction, among them those to pneumococcus and to plague.

IV-1 has been estimated to have a molecular weight of less than two hundred thousand; that in Fraction III-0 of over one million. These lipoproteins are thus totally different chemical substances which presumably serve different functions related to their structure.

*Fraction IV-4* contains a variety of enzymes and hormones, including hypertensinogen and thyrotropin. It has recently been subfractionated to yield a serum esterase, a carbohydrate-rich  $\alpha$ -globulin and the iron-binding protein, presumably responsible for the transport of iron in the plasma.

*Fraction V* contains the human serum albumin that has been made available in such large amounts to the Armed Forces for use in the treatment of shock, hypoproteinemia and edema. As at present released for distribution, under conditions that have been specified by G. Scatchard, L. E. Strong and W. L. Hughes, Jr., it is poor in salt and is so stable in the presence of non-polar anions, developed for this purpose largely by J. M. Luck, that it is heated in the final container for ten hours at 60° C. That these conditions suffice for the destruction of the virus of infectious hepatitis has been demonstrated by J. Stokes, Jr.

*Fraction VI* consists of the large amount of salts, especially citrates, and the small amount of protein left in the mother liquors following the removal of these various precipitates. It should also contain small organic molecules not bound to one or another of the proteins of plasma by specific forces. Most small molecules, for which tests have been carried out, have, however, been found in one or another of the precipitated fractions. Nonetheless, Fraction VI deserves further exploration, as do fractions of proved therapeutic value.

*Distribution* of the various components of plasma into these fractions is graphically represented in figure 2, which indicates accurately the proportions of the proteins separated in each fraction and suggests also the uses that have thus far been found for each.

This distribution may be considered also from the point of view of those physical chemical properties of proteins which may readily be seen to influence their functions in the body. Thus Fraction I has a very pronounced effect on viscosity due to the asymmetric fibrinogen molecules it contains, whereas Fraction V, rich in albumin, has a small effect on viscosity compared with its large effect on osmotic activity, the property which is responsible for drawing fluid into the blood stream and holding it there. Indeed, the osmotic activity of Fraction V is far greater than that of all other fractions combined. The value of the other fractions is clearly greater in conjunction with their more specific chemical properties and physiological functions.

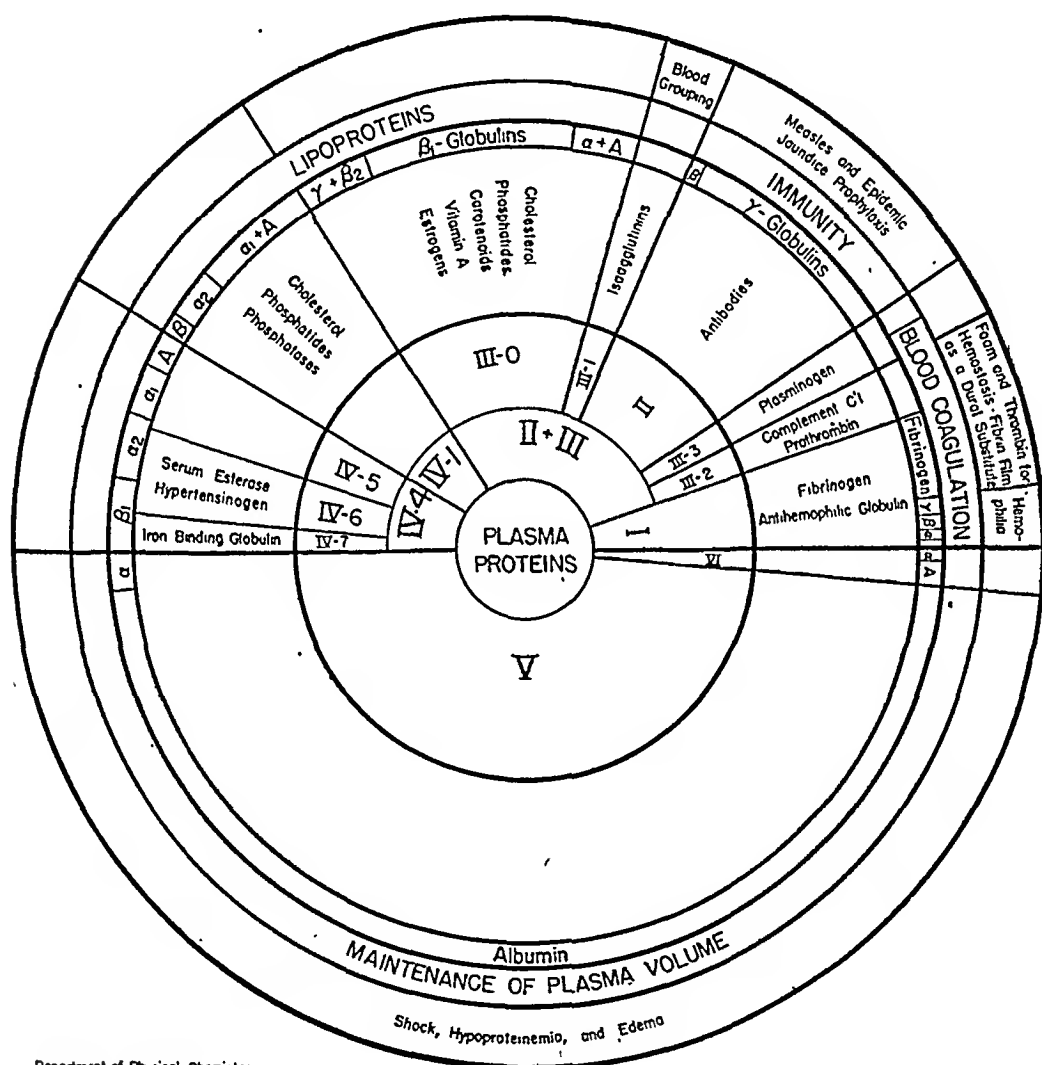
#### IV. THE DIVERSITY OF THE PLASMA PROTEINS

The value of blood in the prevention or treatment of disease depends but rarely upon the whole tissue. Rather it depends upon one or more of the cellular, protein or smaller organic constituents of the blood for which

there is great need. This need is for quite different constituents of the blood in hemophilia or hypertension, measles or anemia, hemorrhage or infectious hepatitis, edema, shock or hypoproteinemia.

## PLASMA PROTEINS\*

### THEIR NATURAL FUNCTIONS AND CLINICAL USES AND SEPARATION INTO FRACTIONS



Department of Physical Chemistry  
Harvard Medical School

FIG. 2.

\* Revised by L. E. Strong from Figure 1, in COHN, E. J.: Blood proteins and their therapeutic value, Science, 1945, ci, 54.

The fractionation of the plasma has made available the albumins for use in shock and the specific globulins of value in measles, hemophilia, blood typing, and blood clotting, has separated also many of the smaller molecules and

has demonstrated that they are not free in the blood stream but are in highly specific, more or less labile, combination with the larger proteins.

TABLE I  
Interactions of Blood Proteins

Protein	Fraction	Interacting Molecule	Origin of Interacting Molecule	Physiological Function
Hemoglobin Carbonic Anhydrase	Red Cells Red Cells	Oxygen Carbon Dioxide	Air Tissues	Respiration
Prothrombin Fibrinogen	III-2 I	Thromboplastin Thrombin	Tissues Prothrombin	Clot Formation
$\gamma$ -Globulins Complement: C'1 C'2 Isoagglutinins	II III-1 III IV III-1	Antigens	Viruses and Bacteria  Red Cells	Immunity
Hypertensinogen Hypertensinase	IV-4 Red Cells and Plasma	Renin Hypertensin	Kidney Hyperten- sinogen	Blood Vessel Constriction
$\beta_1$ -Lipoprotein $\alpha_1$ -Lipoprotein	III-0 IV-1	Estriol, Vitamin A Vitamin A		Lipid Transport
Choline Esterase Serum Esterase Phosphatase (Alkaline)	Red Cells IV-6 IV	Choline Esters Choline Esters* Phosphoric Acid Mono Esters		Ester Hydrolysis
Plasminogen**	III-3	Proteins	Plasma	Protein Hydrolysis
Iron Binding Serum Globulin	IV-7	Iron		Iron Transport

\* Hydrolyzes Methyl Butyrate.

\*\* Fibrinolytic Enzyme Precursor.

Thus, the accompanying table lists specific plasma globulins which have been separated which combine reversibly with iron and presumably transport it to the tissues; which dissolve water insoluble lipids, such as cholesterol, in large amounts; as well as lipid vitamins, such as vitamin A, and lipid hormones, such as estriol. Globulin enzymes with esterase and proteolytic functions have also been separated and concentrated. In other investigations albumins have been demonstrated to combine selectively with organic metal complexes such as mercurials and the sulfa drugs as well as with water insoluble organic molecules such as quinones and long chain fatty acids. The number of specific interactions between the small organic molecules and the large protein molecules that occur in the blood and in other tissues is far greater than has thus far been demonstrated. Their separation as natural protein complexes renders it possible to study the interacting physico-chemical forces, as well as to explore these natural physiological mechanisms and to determine their possible value in therapy.

# THE USE OF GAMMA GLOBULIN FROM LARGE POOLS OF ADULT BLOOD PLASMA IN CERTAIN INFECTIOUS DISEASES \*†

By JOSEPH STOKES, JR., M.D., *Philadelphia, Pennsylvania*

ALTHOUGH the protein fraction of blood plasma termed gamma globulin had been well defined previous to World War II, the product itself has recently assumed a greatly enhanced significance as a result of two practical developments of this war period. These are, first, the development by Dr. Edwin J. Cohn, and his co-workers at the Harvard Medical School, of a method of fractionation of plasma into several of its useful components; and, second, the pooling of plasma for fractionation from hundreds or thousands of blood donors under the system of blood collection inaugurated by the American Red Cross.

The first of these developments has served to emphasize the extraordinary diversity and essentiality of functions furnished to the body by the individual components of the blood plasma. By the method of separation of the gamma globulin fraction developed by these workers, the major portion of the antibodies in adult blood plasma against foreign protein antigens (viruses, bacteria, toxins, pollens, etc.) has been obtained. It must be emphasized that the process of fractionation of gamma globulin not only separates but also concentrates the antibodies.<sup>1</sup> The concentration of antibodies in the gamma globulin thus prepared is approximately 25 times that of normal pooled plasma.<sup>2</sup>

The second of these practical developments, namely the pooling of plasma from hundreds or thousands of adult blood donors, while only of quantitative value in the separation of such plasma components as albumin, may be, and usually is, of great qualitative value in respect to gamma globulin. The presence of antibodies against infectious diseases in human plasma appears to depend upon exposure to antigenic stimuli resulting both from subclinical or inapparent and from clinical infections.

The large size of the plasma pools developed by the American Red Cross tends to assure a surprisingly uniform titer of antibodies against the infectious agents endemic to the geographic area in which the blood donors reside. In studies of gamma globulin obtained from donors in the eastern region of the United States, Dr. Werner Henle of the Children's Hospital,

\* Presented at the Twenty-seventh Annual Session of the American College of Physicians, Philadelphia, May 14, 1946.

† These investigations have been carried out as a project of the Commission on Measles and Mumps, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

We wish to express our great appreciation for the assistance of Mrs. Jeanette H. Levens and Miss Beatrice Payson without whose indispensable contributions in carrying out the technical procedures these investigations could not have been completed.

Philadelphia, found no detectable antibodies against Western equine encephalomyelitis virus, whereas antibodies against the Eastern equine encephalomyelitis virus were found in considerable amounts.<sup>8</sup> We are not aware of any evidence of the opposite picture in the gamma globulin obtained from Western donors, but it is probable that such a contrast would be found. Following the influenza A epidemic of November and December 1943 the gamma globulins from all areas of the United States gave evidence of a marked general increase in the antibodies against influenza A virus. A direct relationship between the height of such antibodies and individual resistance to influenza A has been demonstrated by a number of workers, including our laboratories in Philadelphia.<sup>18</sup> Thus the general level of donor's antibodies in any population may provide an indication of its susceptibility to the epidemic disease as well as evidence of a recent epidemic wave of influenza. The uniformity of antibody levels in pooled plasma and thus in gamma globulin depends chiefly therefore upon the following factors:

1. The presence of endemic or of recent epidemic disease in the geographical area from which the blood is drawn.
2. The amount and the duration of antibodies resulting from specific infections.
3. The number of donors contributing to the pool.

Certain of these factors can be controlled in the collection of pooled plasma.

For a discussion of gamma globulin from pooled plasma it appears important to review some theoretical considerations relating to certain of the epidemic diseases of childhood caused by viruses, and also certain data recently accumulated concerning the possible uses of gamma globulin in such diseases.

The diseases chosen for this particular comparison are: (1) Measles; (2) Mumps; (3) Infectious (epidemic) hepatitis; (4) Poliomyelitis.

Although not demonstrated conclusively in any of these four diseases it appears possible from the facts now available that either apparent or inapparent infection in childhood or early adult life with the four viruses effects a slowly developing permanent immunity to them in the greater part of the general population. Because of its ease of transmission, measles immunizes the general population earlier than the other three diseases. Infectious (epidemic) hepatitis appears to be the least readily transmissible (although it may be present at times in drinking water) of the four diseases and therefore may not immunize most of the population until the age range of approximately 30 to 35 years. Mumps and poliomyelitis would appear to occupy a position between measles and infectious hepatitis, depending upon the ease with which they are transmitted in varying aggregations of individuals. Thus, under usual conditions in the United States larger numbers of frank clinical cases of mumps and poliomyelitis occur among

young adults than is the case with measles. The rapidity with which a population is immunized also obviously depends upon whether it is urban or rural. The unusual aggregations consequent to war-time conditions accelerate the immunization of persons from rural groups. The incidence of frank clinical cases of measles, mumps, infectious hepatitis, and poliomyelitis in the entire population diminishes in the order named. This order of incidence is not theoretical; the facts are well known. In contrast to the incidence of frank clinical cases, it appears possible (a theoretical possibility supported by considerable data) that the incidence of subclinical or inapparent infections increases, rather than diminishes, in the same order, measles having very few and poliomyelitis a great number of subclinical or inapparent cases. If most of the general population throughout its early years is permanently immunized against these infections by an interaction between host and parasite, regardless of whether the interaction is apparent or inapparent, then it is highly probable that the gamma globulin obtained from the general population in an age range above 30 years would contain antibodies in concentrated amounts against all of these diseases. These theoretical considerations have been strengthened by considerable experimental evidence.

Whether or not such concentrated antibodies are present and will passively protect against measles, mumps and infectious hepatitis has been studied in humans. Although no tests have been made in man due to war conditions, considerable evidence from studies of mice, cotton rats and monkeys indicates the presence in gamma globulin from human plasma pools of large amounts of antibodies against certain strains of poliomyelitis virus.

In passing from theory to practice the results of experimental study of these four diseases now may be considered.

*Measles.* In measles the data have been reviewed previously by a number of workers. Studies at the Children's Hospitals in Boston<sup>5</sup> and Philadelphia<sup>6</sup> have indicated that gamma globulin represents the most satisfactory biological as yet developed for passive protection of exposed susceptibles or for attenuation of the disease. The uniformity of antibodies demonstrated against other antigens than measles virus offers considerable assurance that the globulin in general has a constant titer of measles antibodies. The variables encountered in the clinical studies have been very few and in all probability have been associated with differing exposures and with a variation in host resistance.

Conclusive evidence concerning the value of gamma globulin in the treatment of early cases of measles must still await further studies although the data thus far obtained have suggested that the disease may be modified when large doses of globulin are administered in the prodromal stage of the disease, at or previous to the appearance of Koplik spots.<sup>6</sup>

*Mumps.* That the presence of considerable amounts of specific antibodies in pooled convalescent plasma or in gamma globulin may not be sufficient to protect against certain virus diseases has been well demonstrated



in the case of mumps in the experimental monkey by Dr. John F. Enders.<sup>7</sup> Following intraparotid injection of a mixture of equal parts of active mumps virus suspension and convalescent human serum only partial protection against parotitis in monkeys could be demonstrated. When gamma globulin derived from plasma obtained by Lt. Colonel Aims C. McGuinness from mumps convalescent cases was used in similar neutralization tests, somewhat more effective protection in monkeys against the disease was noted. Evidence of the comparative values of ordinary gamma globulin and of gamma globulin derived from the fractionation of convalescent plasma was obtained by Captain Sydney S. Gellis and Lt. Col. Aims C. McGuinness under the Commission on Measles and Mumps, Army Epidemiological Board.<sup>8</sup> As obtained from their data table 1 indicates that when 20 ml. of

TABLE I

Comparison of Incidence of Orchitis in Alternate Cases of Mumps Injected with Convalescent Gamma Globulin—20 ml.—on First Day of Illness with Incidence of Orchitis in Alternate Controls

	No. Patients Who Developed Orchitis	Incidence of Orchitis (%)
No. of injected patients.....51	4	7.8
No. of controls.....51	14	27.4

gamma globulin from convalescent pools were injected parenterally in the first 24 hours after the onset of epidemic parotitis a diminution in the incidence of orchitis to 7.8 per cent occurred, while no significant effect had been obtained from the parenteral injection of 50 ml. of ordinary gamma globulin. In all large outbreaks of mumps in the U. S. Army as well as in the units studied, the incidence of orchitis has approximated 27 to 33 per cent, thus indicating that the protection afforded by the gamma globulin from convalescent plasma was apparently not a chance occurrence, but was a result of the injected material. This difference obtained in the two groups is statistically significant. The obvious conclusion is that the protective antibodies must be administered in considerable amounts to be effective. It remains to be determined whether or not the titer of complement fixing antibody which was considerably greater in the gamma globulin from convalescent plasma (Enders) is an index of the protective value of the material.

Although insufficient evidence is available, apparently gamma globulin from plasma pools derived from the general population is not usually effective in protecting exposed susceptibles against mumps in amounts up to 50 ml. Considerable amounts of complement fixing antibodies in the pooled plasma of the general adult population from whom the blood is drawn and thus in the gamma globulin emphasize the finding of Drs. J. F. Enders and L. W. Kane in Boston, together with Drs. E. P. Maris and J. Stokes, Jr., in Philadelphia<sup>9, 10</sup> that when an epidemic of mumps sweeps through a group of susceptibles in a children's institution, in addition to those who contract

frank clinical cases, there is also a considerable group of susceptibles who suffer inapparent or subclinical infections. The latter group develops complement fixing antibodies and positive skin tests to heated mumps virus for the first time as a result of such inapparent infections and apparently is immunized following such exposure. It is reasonable to suppose that in this manner most of the susceptibles gradually disappear throughout early life as a result of repeated exposures, whether or not they suffer from frank clinical mumps, and in a reciprocal manner, antibodies appear in the general population.

The value of gamma globulin in mumps thus appears to depend upon facilities for the pooling and fractionation of large amounts of convalescent plasma. In time of peace only moderate amounts of convalescent plasma would be available. If this could be obtained, which seems problematical, it should probably be reserved for treatment of adult males in the first 24 hours of their disease with the aim of preventing or attenuating acute orchitis. The equivalent amount of pooled convalescent plasma injected intravenously should be equally effective but is not as readily preserved as the gamma globulin due to required storage facilities and deterioration. Also the risk of producing serum hepatitis apparently is absent in the case of gamma globulin.

*Infectious (Epidemic) Hepatitis.* In measles and mumps, one is dealing with virus agents which can at least be studied in monkeys, if not in other animals. Such is not the case in infectious (epidemic) hepatitis, since no susceptible animal has been found. Also in measles and mumps there appear to be few differences in the antigenic properties of their respective viruses inasmuch as one attack usually confers a permanent immunity against all other epidemic strains of virus. Due to the low incidence of frank cases of infectious (epidemic) hepatitis during times of peace, adequate data concerning the antigenic relation of epidemic strains are lacking. Also the virus agent or agents responsible for homologous serum hepatitis may or may not have an antigenic relationship to infectious (epidemic) hepatitis.<sup>11</sup>

TABLE II

Infectious (Epidemic) Hepatitis and Homologous Serum Hepatitis Comparison

Observation	Infectious Hepatitis	Serum Hepatitis
1. Fever associated with onset	Usually exceeds 100° F.	Seldom exceeds 100° F.
2. Usual interval from exposure to jaundice	20-40 days	60-120 days
3. Secondary cases not related to injection of blood products	Common	Uncommon
4. Human biological materials known to contain causative agent	Feces and blood	Blood
5. Age susceptibility	Uncommon after 40	Apparently common after 40
6. Oral administration of infective serum	+	-
7. Homologous immunity	+	+
8. Heterologous immunity	-	-

TABLE III \*

Studies on Cross Immunity Between Serum Hepatitis Virus (S.H.) and Two Strains of Infectious (Epidemic) Hepatitis Virus (I.H. Pa. and I.H. S.)

Volunteers		Challenge Inoculation		Results		
Status	No.	Virus	Route	No Hepatitis	Questionable Hepatitis	Definite Hepatitis
Previous infection with Virus S.H.	9	S.H.	Parenteral	4	5	0
	5	I.H. Pa.	Parenteral or oral	0	1	4 (80%)
Previous infection with Virus I.H. Pa.	12	I.H. Pa.	Oral	11	1	0
	5	I.H. S.	Oral	5	0	0
	4	S.H.	Parenteral	2	0	2 (50%)
Previous parenteral inoculation with Virus I.H. Pa., without subsequent apparent infection	9	I.H. Pa.	Oral	9	0	0

\* Results of studies pertaining to homologous and heterologous immunity following apparent or possible inapparent infections with viruses SH and I.H. Pa. Expected average incidence of hepatitis in normal persons (no previous inoculations or history of hepatitis) of this age group inoculated with these viruses for the first time were as follows: Virus SH parenteral, 72 per cent; Virus I.H. Pa. oral, 74 per cent, parenteral, 11 per cent; Virus I.H. S. oral, 50 per cent on basis of small control group.

Table 2 indicates some of the differences between these diseases which are now known. Table 3 indicates the results of an experiment described elsewhere<sup>12</sup> on cross-immunity between two strains of infectious (epidemic) hepatitis virus and a strain of serum hepatitis virus, which suggest that the two viruses differ in their antigenic properties. One point appears to be of particular importance, namely, that in infectious (epidemic) hepatitis the incidence rapidly decreases after the age of 30 years, whereas the evidence thus far available does not indicate a similar tendency in serum hepatitis. As previously mentioned, a general immunization of the population during the early years apparently occurs in infectious (epidemic) hepatitis, whereas this may not occur in serum hepatitis. If this occurred in serum hepatitis it would be more difficult to explain the hepatitis resulting from the use of the plasma pools in battle casualties.

The presence of antibodies cannot readily be determined by serological means, as in mumps, and thus one can only infer from epidemiologic evidence and from the protective effect of the gamma globulin (see below) that a major portion of the general population is immunized during the early years of life from apparent or inapparent infection with the virus of infectious (epidemic) hepatitis. The experience during the recent war period with different epidemics of infectious (epidemic) hepatitis suggests that clinical cases without jaundice may be nearly as frequent as those with jaundice.

TABLE IV

Cases of Hepatitis with Jaundice Following Date of Injection with Globulin

Group	Total Injected	Jaundice Cases	Incidence, Per Cent	Total Controls	Jaundice Cases	Incidence, Per Cent
1	406	4	1	683	25	3.7
2	831	3	0.4	8,270	283	3.4
3	495	2	0.4	1,373	27	2.0

Table 4 illustrates the protection afforded against infectious (epidemic) hepatitis by a dose of 10 ml. of gamma globulin in certain units of the 5th Army during the fall and winter of 1944 to 1945. The final results, as gathered later by workers in the field, have demonstrated even more strikingly the value of gamma globulin for passive immunization in this disease. In addition to three epidemics studied with Captain S. S. Gellis<sup>18</sup> and Captain J. R. Neefe,<sup>14</sup> two in the Mediterranean Theatre of Operations and one in the United States, Dr. J. R. Paul of New Haven<sup>15</sup> and Major W. P. Havens, Jr., have reported a similarly favorable result. The protection afforded appears to be effective for a period of from six to eight weeks, inasmuch as the long incubation period offers a more adequate opportunity for passive protection than in such a disease as measles. The protective dosage has been demonstrated to be as small as approximately .06 ml. per pound of body weight, and may prove to be even smaller.

In contrast to the value of gamma globulin in prevention of infectious (epidemic) hepatitis, no value in treatment of the active disease could be demonstrated in limited studies conducted with Captain S. S. Gellis in the Mediterranean Theatre<sup>18</sup> during the autumn and winter of 1944 to 1945. These studies were not sufficient to be conclusive and it was possible to treat only a few cases within the first few days of onset. Treatment of infectious (epidemic) hepatitis with gamma globulin deserves further trial.

The value of gamma globulin in the prevention of serum hepatitis remains an interesting problem. Studies were initiated in two large general hospitals in this country among battle casualties who had received blood or plasma or both at the time of injury in various theatres of war. In one hospital<sup>16</sup> in which alternate casualties were injected with gamma globulin—10 ml. in a single dose—the incidence of hepatitis in the injected group did not differ significantly from the incidence of the disease in the controls. However, the average incubation period in the injected group was significantly longer than the average incubation period in the controls. The chance of this average delay in the incubation period not being due to the injection of the globulin was calculated as approximately one in four hundred. In another general hospital<sup>17</sup> which suffered a considerably higher incidence of serum hepatitis, alternate casualties were injected with two doses of 10 ml. each of gamma globulin at an interval of 30 days. The use of two doses appeared to be considerably more successful than a single dose in that the ratio of cases of hepatitis in the control group to cases in the

injected group was as seven to one. The chance distribution of the alternate cases in this hospital was indicated by the fact that the various percentages of casualties from the three different theatres of war—European, Mediterranean, and Pacific—were almost identical in the injected and control groups. The only additional general hospital from which data have been obtained as to the results of a single injection of gamma globulin, 10 ml. in all transfused battle casualties reported that the average incubation period of all cases of serum hepatitis was considerably increased over the average incubation period in those cases which occurred before the use of gamma globulin was started. Such data are difficult to evaluate until there is an opportunity of studying further the effect of multiple or larger doses of the globulin in controlling the disease.

In view of the fact that the incidence of infectious (epidemic) hepatitis falls off rapidly after approximately 30 years of age and that no such change has been demonstrated in serum hepatitis, it is difficult to believe that gamma globulin from large pools of adult plasma would be as highly effective in serum hepatitis as in epidemic or infectious hepatitis.

*Polio myelitis.* When gamma globulin from the American Red Cross pools became available, Dr. Sydney Kramer at Michigan, and Dr. Werner Henle and I in Philadelphia were all equally interested in determining the presence of neutralizing antibodies against the Lansing strain of poliomyelitis virus. Neutralization tests were conducted in both laboratories when the material first became available and the presence of large amounts of such antibodies was demonstrated. It also became apparent that a very small amount of gamma globulin, 0.1 ml. injected intraperitoneally, would usually protect a mouse, even when the virus was injected intracerebrally at the same time. Further studies conducted by Kramer in cotton rats and monkeys have confirmed its protective value in these animals similar to that originally demonstrated in mice.

The interest in these findings lies not so much in their practical application, which appears highly problematical in view of the low incidence of the disease in man, but rather in the fact that despite the low incidence of the clinical disease, the relatively large amounts of antibodies present would suggest an immunization of the general population, which could perhaps best be explained by subclinical or inapparent infections. This also confirms earlier antibody studies by Kramer<sup>18</sup> and Aycock.<sup>19</sup> There are obviously other possible explanations which in view of the present findings appear less plausible.

Due to the expensive and time-consuming neutralization test in mice, cotton rats, or monkeys, and the variation in virus strains one can only infer, as in infectious hepatitis, on epidemiologic evidence and from the protective effect of the gamma globulin that immunization of a major portion of the general population occurs during the early years of life from mild clinical or subclinical (inapparent) infections. In poliomyelitis this point remains of major importance for investigation, namely, to determine

at what age in different geographical areas antibodies appear in groups of children studied longitudinally and both individually and collectively.

In animals, treatment with gamma globulin has proved totally ineffective and injection of large amounts of gamma globulin during the incubation period even well in advance of the earliest onset of the disease has not appeared to decrease its severity when the virus is injected intracerebrally.

During a recent severe epidemic of poliomyelitis Perkins and Bahlke<sup>20</sup> of the New York State Department of Health demonstrated that large doses of gamma globulin injected parenterally as treatment in alternate preparalytic cases had no effect on the course or outcome of the disease. The use of large amounts of gamma globulin for the study of passive protection of animals infected by more natural routes deserves continued investigation.

*Rubella.* Due particularly to the serious consequences to the fetus often attendant upon rubella in the mother during early pregnancy, as first reported from Australia by N. M. Gregg<sup>21</sup> and confirmed by many other workers, passive protection against this disease in the pregnant woman assumes an added significance. In 1943 and 1944 two experiments on rubella were conducted in Philadelphia, one at the University of Pennsylvania Hospital and one with Dr. Waldo Nelson at Temple University Hospital. In the first study, a nurse with rubella intimately exposed five room-mates who had no history of the disease. No secondary cases developed following the injection of 5 ml. of gamma globulin four days after exposure in each of the presumably susceptible adults. In the second study, an infant with rubella intimately exposed to the disease a ward of 13 infants and children who were presumably susceptible. No secondary cases developed following the injection of 2 ml. of gamma globulin four days after exposure. These results are recorded only for the purpose of suggesting the need for additional studies in this field. As in the other diseases mentioned, the major portion of the population appears to be immunized in early life.

### CONCLUSIONS

1. Many epidemic diseases of childhood gradually immunize the general population both by apparent and inapparent cases and leave in passage considerable amounts of antibodies in adult plasma.
2. When such adult plasma is pooled from thousands of individuals it probably contains fairly uniform titers of antibodies, the changes in which, if readily measurable, afford an index of epidemic trends.
3. Gamma globulin from fractionated pools of plasma concentrates and preserves such antibodies in a readily usable form, which thus far apparently has been free from the danger of serum hepatitis.
4. The amount of specific protective antibodies in the gamma globulin and their effectiveness against each epidemic disease obviously differs and must be determined in each disease. In certain epidemic diseases outlined, they are highly effective.

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# HEMOPHILIA: THE CLINICAL USE OF ANTI-HEMOPHILIC GLOBULIN \*

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THE beneficial effect of whole blood transfusion in hemophilia has been recognized for over 30 years. The marked fall in the coagulation time following the transfusion of normal blood was attributed in 1916 by Minot and Lee<sup>1</sup> to the platelets. Patek and Stetson reinvestigated the problem in 1936. They confirmed the findings of Minot and Lee but showed that plasma free of formed elements including blood platelets had an effect similar to that of whole blood. Patek and Stetson proposed the thesis that the beneficial effect of whole blood transfusion in hemophilia was due to a factor or factors residing in the blood plasma. The prolonged coagulation time in hemophilia was due in the opinion of these authors to a deficiency of the plasma factors.

In a series of reports from the Thorndike Memorial Laboratory over the past 12 years it has been shown that the antihemophilic property of platelet free plasma was closely associated with the globulin fraction of the plasma proteins. It has also been shown that the antihemophilic factor is neither prothrombin nor fibrinogen. Globulin fractions of normal human plasma were prepared free from both prothrombin and fibrinogen which had optimal effect in reducing the prolonged coagulation time of hemophilic patients to normal both in vitro and in vivo.

As E. J. Cohn has intimated, during the war large quantities of the plasma globulins obtained as a by-product from the preparation of human albumin, became available for physiologic study. In vitro studies of Cohn's fractions<sup>2</sup> showed that Fractions I, II and III had marked antihemophilic activity. Fraction IV had on occasion slight activity while Fraction V, the albumin fraction itself, had none.

Since it was known that Fraction I, that is, the fraction containing from 60 to 90 per cent of fibrinogen, could be injected into humans, in vivo studies were commenced on this fraction.<sup>4</sup> There is no implication that Fraction I is the best source of antihemophilic potency but its availability in sterile dried form offered a convenient starting point for investigation. As shown in figure 1 as little as 11 mg. of Fraction I injected intravenously into a case of hemophilia caused a marked drop in the coagulation time, whereas amounts of between 200 and 400 mg. gave optimal effects. The injection of preparations of Fraction I were comparable in their antihemophilic effect with those obtained following the injection of whole blood or plasma (figure 2).

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The effect of intramuscular injections of Fraction I seems to be unpredictable when administered to adult patients even when massage and heat are used at the site of injection.

Fraction I contains the fibrinogen of blood plasma as well as small amounts of prothrombin. Since our earlier work<sup>5, 6, 7, 8</sup> indicated that neither of these proteins was responsible for the antihemophilic properties of plasma, it was important to remove these substances from Fraction I. This step was accomplished by heating a solution of Fraction I to 56° C. for five minutes and filtering. The filtrate contained no fibrinogen and only traces of prothrombin. However, it was as active as a source of antihemophilic activity as the whole fraction from which it was prepared. This

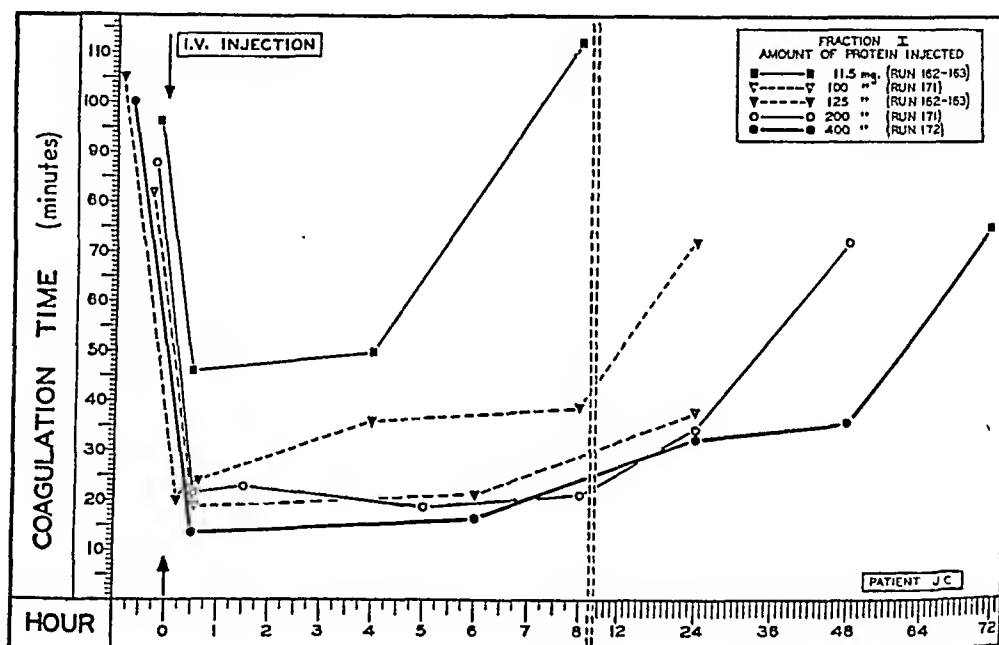


FIG. 1.

observation makes it probable that the antihemophilic property of plasma may be concentrated in a few milligrams of material, offering possibly an opportunity for a therapeutic approach to hemophilia.

At the present time two important matters must be clearly understood. The preparations of Fraction I vary a great deal in their antihemophilic potency. This can only be remedied after further study of the preparations in order to obtain satisfactory criteria. Secondly, as increased purity is obtained some cases of hemophilia fail to respond to the injection of Fraction I although they respond to crude preparations of plasma proteins and to plasma. It has been assumed for some years that the deficiency in hemophilia is not necessarily a single factor. Therefore, in patients who fail to respond to Fraction I, other of the globulin fractions must be investigated as soon as suitable preparations for intravenous human use are obtained.

The injection of Fraction I may be used in the preparation of patients with hemophilia for dental extraction. The use of Fraction I for the control of hemorrhage in hemophilia is under investigation. A much more extensive clinical trial is necessary to evaluate the usefulness of the preparation for this purpose. The results so far have been promising. No refractory phase has been obtained following the injection of Fraction I and no untoward reactions following the injection of the material have been observed. The dose of the material required to control hemorrhage varies from patient to patient. At present 400 mg. of the material in 20 c.c. of isotonic salt solution is used as an initial dose. In preparing patients for operative procedures multiple injections may be employed on the day pre-

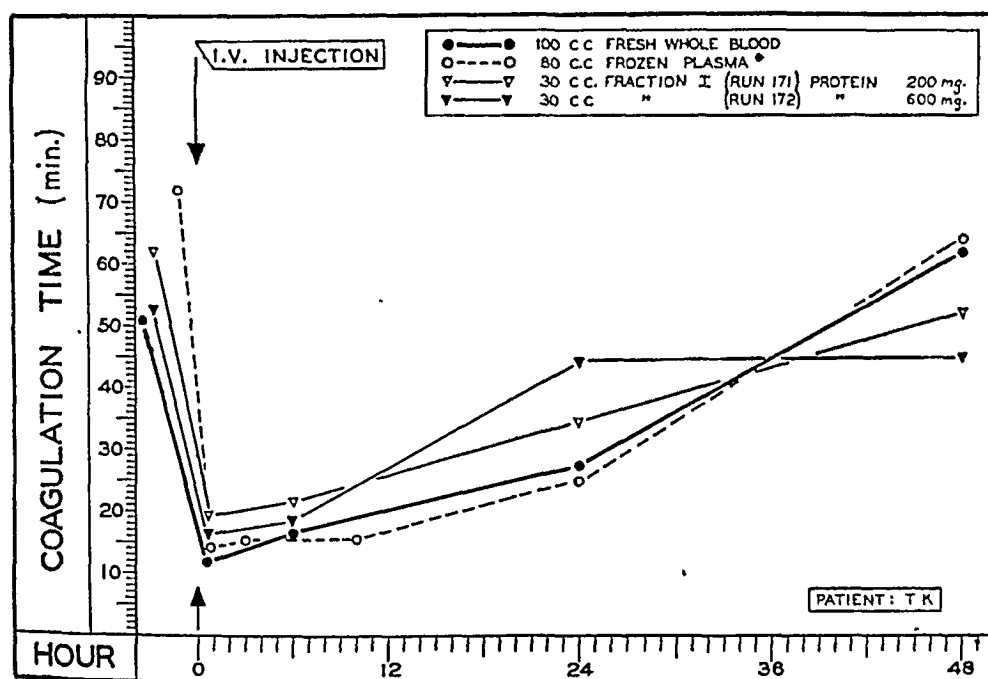


FIG. 2.

ceding the operation. However, if the patient is already anemic due to repeated hemorrhage, it is essential that whole blood be used rather than only plasma or antihemophilic globulin.

Of equal importance to the control of the blood coagulation time, in hemophilia, is the control of local hemorrhage when it occurs. The availability of a good hemostatic agent for this purpose is desirable. Antihemophilic globulin has some hemostatic properties. However, since this material produces clotting of blood by activating the blood coagulation reaction, its effects require a matter of minutes to develop. On the other hand, thrombin preparations which act directly on fibrinogen to produce fibrin clots require only seconds to produce this effect. For this reason, thrombin is an ideal hemostatic agent.

As Dr. Cohn has pointed out, preparations rich in prothrombin can be obtained by suitable fractionation of the plasma globulins. Prothrombin can be converted to thrombin by interaction with tissue thromboplastin derived from brain, lung, placenta or other tissues. The thrombin so obtained may be spread on or impregnated into sterile gauze, fibrin foams or absorbable cellulose and applied with pressure to the bleeding point. It is important that the highest possible concentration of thrombin be applied to the lesion. For this reason we favor the direct application of packs containing powdered thrombin rather than liquid preparations which may wash away rather quickly from the wound. Preparations of human thrombin and absorbable non-reactive sponges are of importance for use in wounds which later are to be closed by suture. For open local hemostasis thrombin from animal sources may be employed.

The application of animal thrombin to local wounds has been employed for some years in our clinic with no indication of local or systemic sensitivity reaction.

A thrombin preparation has been made by Parfentjev from rabbit plasma by simple salting out procedures requiring no activation with thromboplastin. We have made similar preparations from the plasma of swine, steers and humans.<sup>9</sup> This preparation is available under the commercial name of "Hemostatic Globulin" and is an extremely potent hemostatic agent. Thrombin preparations *must never* be injected parenterally due to the fact that they can produce intravascular clotting and profound shock.<sup>10</sup>

The availability of thrombin preparations has reduced enormously the risk of surgical procedures among hemophilic patients. Prior to the development of powerful hemostatics, simple procedures such as dental extractions in hemophilic patients were attended by at least the risk of profound anemia. Since the use of thrombin in our hemophilic clinic over the past ten years, bleeding has been well controlled following operative procedures, such as dental extractions, amputation and skin grafting and no serious sequelae have developed.

Further progress may be noted in the development of therapeutic agents for the treatment of hemophilic hemorrhage. Material for this purpose which may be contained in a small enough volume to permit its prophylactic use by hemophilic patients is an ultimate aim. Such material may be used to advantage in the preparation of hemophilic patients for operation. So far our experience along these lines has been with the use of our own globulin preparations and Fraction I of Cohn. Standardization of the commercial methods of preparation of this substance is required and a careful assay of the *in vivo* activity of other fractions is necessary.

In addition to decreasing the coagulation time of hemophilic blood by the use of globulin preparations, progress has been made in the development and utilization of thrombin preparations for the control of hemorrhage. The introduction of such hemostatics has markedly lowered the dangers attendant upon surgical operations on hemophilic patients.

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# OTHER USES OF PLASMA FRACTIONS WITH PARTICULAR REFERENCE TO SERUM ALBUMIN \*

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## INTRODUCTION

Most clinical studies with plasma fractions thus far have been based on knowledge concerning the physiology of the plasma proteins which was already available, so that investigation has consisted of the verification of predictions which could be made on a priori grounds. In the future, however, the studies should enter a more exciting phase when we shall be exploring unknown territory. Cohn<sup>1</sup> has discussed a rather new conception of the function of the plasma proteins, namely, their importance as vehicles for the transport of substances of low molecular weight or of water-insoluble lipoids. He has also indicated that it is possible to separate certain fractions from the plasma globulins, in which hormonal or enzymatic activity, such as that of serum esterase, is very highly concentrated in comparison with pooled normal plasma. The clinical and physiological importance of such proteins as the serum globulin with esterase activity, the  $\beta$ -globulin with capacity to bind free iron, and the lipoproteins of plasma, is a field for investigation which opens up many inviting prospects. At present we are only in the initial stages, when the all-important work of determining the safety of these preparations for clinical use is just beginning.

## USES OF THE GLOBULIN FRACTIONS

Stokes<sup>2</sup> has indicated the progress which has been made in the application of a highly purified gamma globulin fraction, containing most of the antibody activity of pooled plasma, to the control of infectious diseases. Minot and Taylor<sup>3</sup> have summarized the present status of investigations with a fibrinogen fraction, in which there is found that component of the normal clotting mechanism which appears to be deficient in the plasma of most patients with hemophilia. Before proceeding to a discussion of serum albumin, certain other products of the fractionation of human plasma deserve a brief word. Although Fraction I is of interest to medical men because of its anti-hemophilic activity, it is of far greater interest to surgeons because of its content of fibrinogen. In combination with human thrombin, derived from Fraction III, it has been used to promote adherence of skin

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grafts,<sup>4</sup> and to form a coagulum around calculi in the renal pelvis so as to effect their complete removal without fragmentation.<sup>5</sup> In the form of fibrin foam with thrombin the clotting proteins have been widely and successfully used to accomplish rapid hemostasis in neurosurgical<sup>6</sup> and certain other surgical procedures.<sup>7</sup> Fibrin film has provided the surgeon with a pliable, transparent, and relatively tough membrane which does not excite a significant tissue reaction but which is gradually replaced with connective tissue without the formation of adhesions to underlying structures. These properties have made it very valuable to the neurosurgeon as an aid in the repair of operative or traumatic defects of the dura mater.<sup>8</sup> The anti-A and anti-B isoagglutinins and anti-Rh globulin derived from Fraction III-1 by concentration of this activity from pooled group-specific or anti-Rh plasma<sup>9, 10, 11</sup> provide potent, dependable reagents for grouping blood which should increase the safety of transfusions of either whole blood or of resuspended red cells.

### USES OF THE ALBUMIN FRACTION

Plasma fractions have contributed to medical progress in two ways: first, as new therapeutic agents, with which it is possible frequently to attain certain objectives which cannot be readily attained with the plasma from which they are derived; and second, as new tools for the study of physiological and pathological processes. The various studies on serum albumin, although by no means complete, illustrate this dual rôle of plasma fractions very clearly.

### ALBUMIN AS A THERAPEUTIC AGENT

Normal human serum albumin was primarily developed, in response to an urgent request from the Armed Forces, as a blood substitute for use in traumatic shock. Because its chemical properties make possible its distribution in a stable, concentrated solution, it is compact to transport and convenient to use.<sup>12</sup> Moreover, the stability of salt-poor albumin in its new diluent, containing but 0.3 gram per cent of sodium and .04 M acetyl-d-l-tryptophane for stabilization, is so great that it can be heated for 10 hours at 60° C. in the final container before distribution.<sup>13</sup> This has made it possible to eliminate any preservative with potential injurious effects, such as the mercurials and should, we believe, obviate the possibility of transmission of viruses, such as the agent of homologous serum jaundice. Clinical experience has also shown that with the elimination of practically all of the globulins, albumin solutions rarely give rise to any immediate reactions, other than occasional pyrogenic reactions or those dependent on their physiological property of increasing plasma volume.<sup>14</sup> In this connection it is worth emphasizing that concentrated albumin, unlike concentrated plasma or gelatin, is only as viscous as whole blood with a hematocrit reading of 50 per cent,<sup>15</sup> and when injected lowers blood viscosity owing to hemodilution. This probably accounts for the fact that it appears to be

more readily tolerated by patients with mild congestive failure than whole blood or other more viscous colloidal solutions.

In the treatment of shock, albumin appears to be an effective blood substitute. Stead and Ebert<sup>16</sup> demonstrated that, if blood was removed rapidly by venesection from human subjects and concentrated albumin administered, there was a much greater increase in plasma volume than could be accounted for by the solution injected, indicating transfer of fluid into the circulation due to the osmotic effect of the albumin. In studies on a larger group of subjects, it was shown that the increase in plasma volume in such experiments approximated closely that expected on the basis of osmotic pressure measurements *in vitro*.<sup>17</sup> In several clinical studies on the use of albumin in shock<sup>18, 19, 20</sup> the expected results were obtained, namely increased plasma volume as shown by hemodilution or by dye measurements and clinical improvement. Studies of circulatory dynamics in shock patients receiving albumin showed that improvement after albumin therapy was associated with an increase in cardiac output,<sup>19, 20</sup> which was greater than that produced by the administration of whole blood.<sup>20</sup> This greater increase in output was interpreted as evidence of the fact that when traumatic shock, due primarily to loss of blood, was treated with albumin (or plasma) the deficit in blood volume was made good, but the patient was left with an anemia, necessitating a more rapid circulation of the remaining hemoglobin to provide oxygen for the tissues.

Fears concerning the use of albumin in the treatment of shock have arisen in the minds of many physicians primarily because they have failed to appreciate that, although it is distributed in 25 per cent solution for convenience, it does not have to be used in that form. There is abundant experimental and clinical evidence that when concentrated albumin is administered to patients with diminished blood volume due to hemorrhage, trauma, or burns, it usually produces both clinical improvement and a considerably greater increase in plasma volume than can be accounted for by the volume of solution injected. However, the administration of additional saline enhances the effect of albumin (table 1). In severely dehydrated patients in shock, already depleted of water or of water and electrolytes, it is obvious that the administration of colloid alone will not suffice to restore the circulation. It should be emphasized that there is no evidence that concentrated albumin is harmful even in severe dehydration, presumably because of its comparatively low viscosity. The experimental work of Fine and his colleagues<sup>21</sup> has confirmed these conclusions and has demonstrated that in dogs additional fluids may be administered to supplement concentrated albumin by way of the gastrointestinal tract or by vein with the albumin. A 5 per cent albumin solution in 0.85 per cent saline solution is approximately isosmotic and isotonic with citrated human plasma. Therefore each 100 c.c. of 25 per cent albumin solution should be supplemented with 400 to 500 c.c. of saline solution, when possible, in the treatment of shock.

TABLE I

Osmotic Effect of Concentrated Albumin  
From Plasma Volume Measurements Made within 1½ Hours of Injection of Albumin

Type of Case	No. Cases	Plasma Volume Increase c.c./gram of injected albumin	
		Spread	Average
Calculated from osmotic pressure measurements <sup>1</sup>			18
Experimental hemorrhage in man <sup>2</sup>	11	13.2-24.1	17.4
Clinical shock <sup>3</sup> ( <i>no additional saline or small amount</i> )	63	0-31.7	11.7
Clinical shock <sup>3</sup> ( <i>additional saline</i> )	20	7-29	17.9

<sup>1</sup> SCATCHARD, G., BATCHELDER, A. C., and BROWN, A.: The osmotic pressure of plasma and serum albumin, Jr. Clin. Invest., 1944, xxiii, 458-465.

<sup>2</sup> HEYL, J. T., GIBSON, J. G., II, and JANEWAY, C. A.<sup>17</sup>

<sup>3</sup> From published data of Cournand, A., Noble, R. P., Breed, E. S., Lawson, H. D., Baldwin, E. Def., Pinchot, G. B., and Richards, D. W., Jr.<sup>20</sup> and Warren, J. V., Stead, E. A., Jr., Merrill, A. J., and Brannon, E. S.,<sup>19</sup> and unpublished data from a study of albumin carried on under direction of Dr. Dickinson Richards for the Committee on Medical Research. Data collected by Cournand and Lowell, Stead and Warren, and Evans.

Experience during the war has demonstrated that traumatic shock, in military or civilian practice, is primarily due to loss of whole blood, unless plasma loss due to burns or peritoneal irritation occurs. Hence optimal treatment requires the use of whole blood to avoid the anemia which develops if plasma or albumin is administered for replacement.<sup>20</sup> The latter two agents may be very useful for emergency supportive therapy, and, despite a recent report in which concentrated albumin was compared unfavorably with isotonic plasma,<sup>22</sup> there is no reason why albumin with saline, either by vein or by mouth, if it can be taken, should not be quite as satisfactory as the latter.

While albumin should be supplemented with fluids in the treatment of shock, in hypoproteinemic edema concentrated low-salt albumin provides exactly that combination of properties needed for rational therapy.\* Certain general statements concerning the use of albumin in hypoproteinemia may be made on the basis of present experience. First, the patient should be on a high caloric diet, with an adequate protein intake, if possible, in order to avoid utilization of the injected albumin as a source of energy. Second, doses of 50 grams daily should be used in adults unless there is congestive failure. This may be given in two doses or mixed with 200 to 300 c.c. of

\* Clinical experience with the use of albumin in the many conditions encountered in civilian medicine where its value might be anticipated has of necessity been quite limited by the fact that albumin was developed and produced for the Armed Forces as a blood substitute during the war. At present albumin can only be obtained from one commercial laboratory, although it may be available before long in two states as a result of their blood programs. The statements about albumin in hypoproteinemia are based on a very limited experience with a fairly small number of patients, and further careful clinical investigation is urgently needed to define the place of albumin in therapy more exactly.



10 per cent glucose and infused by intravenous drip over a period of several hours. Third, a considerably larger amount must be given than would be expected on the basis of the deficit in circulating albumin. Fourth, injected albumin will not ordinarily appear in the urine unless there is proteinuria already.

Hypoproteinemia is rarely the result of a single factor, but usually of a combination of inadequate food intake, protein loss, and increased catabolism incident to serious illness, injury, or surgical procedure. Abundant food is obviously the best treatment for hypoproteinemia, while intravenous alimentation with a solution of amino acids or hydrolyzed protein is rational as a supplement to or substitute for oral feeding when necessary. However, there are times when it is important to relieve edema promptly in order to promote healing or to relieve symptoms, such as obstruction at an intestinal anastomosis, pulmonary congestion, or circulatory inadequacy with oliguria when these are the result of hypoproteinemia. Before the introduction of albumin, the clinician was well provided with solutions—glucose, saline, and sodium lactate or bicarbonate for repair of dehydration and acidosis but he was not well equipped to deal with edema. Plasma has certain drawbacks—first, the large amount of water and sodium salts which must be given with the protein, second, the fact that only half its protein is albumin, which has the greatest osmotic activity, and third, the chance that it may give rise to homologous serum jaundice in an occasional recipient. In a few patients with acute but reversible hypoproteinemia, the administration of albumin in large doses has elevated the level of serum albumin rapidly with diuresis, even during periods of increased catabolism when intravenous amino acids produced little benefit.<sup>23, 24</sup> This should make albumin very useful to internists, surgeons, pediatricians, and obstetricians, all of whom frequently see patients who need prompt relief for hypoproteinemic edema. In addition to the relief of generalized edema, albumin deserves further study as a means of controlling local edema in such sites as the brain, lungs, and gastrointestinal tract where it gives rise to symptoms. Little is known of its usefulness under these circumstances.

Hypoalbuminemia is a frequent accompaniment of diffuse disease of the liver. In cirrhosis, intravenous albumin, in doses of 25 to 50 grams daily in addition to an adequate diet, will raise the serum albumin level to normal in one to two weeks. This change in serum proteins is associated with an increase in sense of well-being, disappearance of peripheral edema, and usually some diminution of ascites.<sup>14, 25, 26</sup> In advanced cases there is apt to be a fall in serum albumin with a gradual return of symptoms when treatment is discontinued. In patients with hepatitis, the lesions in the liver are reversible, and albumin therapy has been used with great benefit when it was indicated by the occurrence of hypoalbuminemia.<sup>27, 28</sup>

Of all types of edema none is so stubborn nor so unpredictable as that associated with the chronic stages of renal disease. Patients may remain bedridden for months on end and then suddenly, for no apparent reason,

begin to exhibit a profuse diuresis. There is little doubt of the importance of reduced colloid osmotic pressure in the production of this form of edema, and hence albumin would appear to be the obvious physiological diuretic agent. That concentrated albumin, and particularly salt-poor albumin, will produce a diuresis in many patients with the nephrotic syndrome, much as acacia does but without its harmful after-effects<sup>25, 29</sup> seems clear from the accumulated experience so far. However, it is equally clear that diuresis does *not* follow albumin administration in certain patients, that it usually lasts only as long as albumin is administered,<sup>30</sup> and that massive doses of albumin (50 grams daily for 20 to 30 days in an adult) are needed to rid the patient of edema and to produce any significant rise of the plasma protein level.<sup>25</sup> A large part of the albumin injected appears in the urine during the 48 hours after a single injection.<sup>29, 31</sup> Thus, the use of albumin in nephrosis is exceedingly wasteful, but deserves further study in cases which are resistant to simple methods of treatment. It should be added that there are those who believe that the massive proteinuria which occurs with albumin therapy may in itself produce kidney damage.

In acute renal failure albumin may be very useful.<sup>32</sup> If oliguria is the result of the poor renal circulation arising from hypoproteinemia and not of primary kidney damage, it may mobilize water and allow the kidney to function. If oliguria or anuria is the result of primary renal damage, as in acute nephritis or sulfadiazine intoxication, albumin may be used to maintain an adequate serum protein level without elevation of the non-protein nitrogen, provided sufficient calories are administered to spare protein catabolism. This is in line with the present feeling that the best treatment for anuria is to keep the chemical composition of the body fluids as normal as possible by parenteral and oral administration of carbohydrate, fluid, and electrolytes under rigid laboratory control.<sup>33</sup> Thus the patient is kept alive until spontaneous repair of the renal lesion leads to a return of the excretory function.

#### ALBUMIN AS AN EXPERIMENTAL TOOL

For short-term physiological studies in animals, bovine albumin, crystallized by the method of Cohn and Hughes<sup>34</sup> is an ideal experimental colloid. Its physical properties are well known and standardized, and, being almost completely free of globulins, its injection does not produce the immediate reactions seen when bovine plasma is given to dogs. It has been used in a series of fundamental studies on the hemodynamics of shock. Fine and his colleagues have used it to investigate the relative importance of colloid and saline in the therapy of tourniquet shock<sup>21</sup> and also the importance of blood viscosity in the irreversibility of shock.<sup>35, 36</sup> Other workers have used crystallized bovine albumin in investigations on various aspects of experimental burn shock.<sup>37</sup> Chemists have found in bovine albumin a pure protein conveniently available for investigations on such problems as the interaction of proteins with other substances and the despeciation and denaturation of proteins.<sup>38</sup> It has been used to provide a

medium of controlled density for studies on the size of virus particles in work which has important practical bearing on the preparation of virus vaccines.<sup>39</sup>

The introduction of human albumin into medicine has provided the clinician with a tool for attacking certain aspects of the pathogenesis of edema which have been in dispute for many years. Previously our knowledge of the function of albumin has been gained principally from the observation of those slow, spontaneous changes which occur in the natural course of disease. Thus, clinical observations on patients with cirrhosis of the liver have indicated that lowering of the serum albumin was an important factor in the production of ascites.<sup>40</sup> Such observations are similar to those made by endocrinologists when ablation of a particular gland was the only available method for experimental study of its function. With the development of potent hormone preparations, the problem could be defined much more clearly by trials of substitution therapy. When albumin has been given to a few patients with cirrhosis until normal levels of serum albumin have been achieved peripheral edema has disappeared very rapidly, while ascites has diminished much more slowly. This indicates that other factors than a lowered colloid osmotic pressure of the blood are important in the production of ascites, among them back pressure in the portal vein, changes in the absorptive power of the peritoneal surfaces, and antidiuretic substances.

In the case of nephrosis, the use of albumin has helped to clarify but not to solve the problem of edema formation. The fact that "spontaneous diuresis" following infection may produce a far greater outpouring of urine than the administration of enough albumin to produce a more striking though temporary increase in serum albumin suggests that water balance is under the control of factors other than the serum albumin level in this disease. During albumin therapy, nephrotic patients excrete greatly increased amounts of protein in their urine. By fractionation of a large amount of urine collected from a nephrotic patient during a period of treatment,<sup>29</sup> an albumin fraction was obtained which appeared to resemble normal human serum albumin in its physical and immunological properties, although it was very toxic when injected into animals. This suggests that the nephrotic cannot retain normal serum albumin and is evidence for the concept that proteinuria is due to a renal lesion rather than to a defect of the plasma proteins. Much more extensive work along such lines as these will have to be done, but these examples serve to illustrate the way in which purified plasma proteins may be used to develop understanding of the pathogenesis of important physiological disturbances in disease.

#### SUMMARY

The use of serum albumin in treatment and investigation has been reviewed. There are gaps to be filled in, but enough has already been done to show how concentrated human albumin provides the clinician with an important therapeutic agent for emergency use in shock and for the treatment

of hypoproteinemic edema, and the investigator with a valuable tool for the study of those conditions in which the concentration of this component in plasma is disturbed.

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# BRONCHIOGENIC CARCINOMA; AN ANALYSIS OF 343 CASES\*

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PRIOR to 1933 when Graham reported the first successful pneumonectomy for bronchiogenic carcinoma, the disease was considered rare. Diagnostic methods were inadequate, there was no curative treatment and interest in the subject was entirely academic. Hundreds of successful pneumonectomies have now been performed by many surgeons. But a careful study of large groups of cases reveals an appalling and unnecessarily low incidence of operability. There are, unfortunately, two periods of delay during which periods the patient may forfeit his chance for cure. The first is between the onset of symptoms and medical consultation and the second is that between the *first medical consultation and a positive diagnosis*. Further improvement in results can come only with a reduction in the total time between the onset of symptoms and the institution of treatment. Careful analysis of large groups of cases must be made in an effort to bring out data which will be helpful in eliminating or reducing to a minimum these periods of delay. Several such reports have appeared recently.<sup>1, 2, 3</sup> With this in mind, a careful survey was made of 343 cases of pulmonary carcinoma from various services at the University of Michigan Hospital. This communication is a report of the results of that study. The cases cover the six year period from January 1, 1938 to January 1, 1944.

For purposes of study, the cases have been divided into two groups. Group 1 comprises 112 cases in which histologic confirmation was lacking although clinically and roentgenologically the diagnosis of bronchial cancer was justified. Several factors entered into the inability to secure adequate confirmation of the diagnosis; the disease had progressed too far to warrant further study, the patient refused further examination or there was a peripheral type of lesion which was inaccessible to bronchoscopic vision. No detailed study was made of this group. Group 2 consists of 231 cases, histologically confirmed, and is further divided into two sub-groups: (1) those who were considered inoperable at the time of the diagnosis or those who refused surgery, and (2) those who had operation, either resection or exploratory thoracotomy. Group 2 cases are considered in detail.

## INCIDENCE

That the increased incidence of bronchiogenic carcinoma is both relative and absolute is an accepted fact. Many articles in support of this have appeared in the past few years and the reader is referred to the recent article by

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Ochsner, Dixon and DeBakey<sup>1</sup> for a splendid inclusive review of the literature and complete bibliography on the subject.

During the six year period covered by this study there were 177,005 registrations at the University Hospital. This includes both in-patients and out-patients. The incidence of bronchiogenic carcinoma in this group is given in table 1 where it may be compared with the incidence during the preceding five year period, 1933-1938.<sup>4</sup>

TABLE I  
Incidence of Bronchiogenic Carcinoma  
University of Michigan Hospital

	Registrations	Bronchiogenic Carcinoma	Cases Proved Histologically	Incidence Per 10,000 Cases	Increase Per 10,000 Cases
1933-1938	152,150	137	100	8.99	
1938-1944	177,005	343	231	13.00	4.01

*Sex.* It is a widely accepted fact that bronchiogenic carcinoma is predominantly a disease of the male sex. Various collected series of cases show the occurrence in men to be from 70 to 90 per cent of all cases.<sup>1, 2</sup> In the 100 proved cases in the early University Hospital series, 82 per cent were males. In the present series, 83.6 per cent of the inoperable cases and 90.0 per cent of the operable group were men.

*Age.* Carcinoma, whether of the lung or elsewhere, is essentially a disease of advancing years with the majority of cases occurring between 40 and 60 years of age. In the group under discussion, the youngest patient was 18 years of age and the oldest was 77. Age, per se, appears to have no effect on operability. Table 2 gives the age incidence by decades.

TABLE II  
Age Incidence  
(231 Proved Cases)

Under 20		20 to 30		30 to 40		40 to 50		50 to 60		60 to 70		Over 70	
No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
2	.86	2	.86	14	6.1	64	28.8	97	41.9	47	20.3	5	2.2

## ETIOLOGY

Much has been written about various factors which have been thought to play a part in the causation of pulmonary carcinoma.<sup>1</sup> The present study adds nothing to support any existing theories of etiology. However, the wide variety of recorded occupations does confirm the conclusion of others, that bronchiogenic carcinoma is not an occupational disease.

## PATHOLOGY

Our conception of the pathology of pulmonary cancer has changed materially in the past 10 years. Prior to the development of resection, autopsy material was the chief source of study. Obviously most of these cases were late and unsuited for a study of the development and early manifestations of the disease.

The right lung is more frequently involved than the left. In the 343 cases included in this study, 203 or 59.2 per cent were located on the right side, 138 or 40.2 per cent on the left and in two cases or 0.6 per cent there was bilateral involvement. In a series of 4,732 cases collected from the literature by Ochsner,<sup>1</sup> 58.3 per cent of the tumors were in the right lung and 41.6 per cent were in the left lung.

Two main types of growth are recognized according to location in the lung, those which occur in the hilus and those which originate in the periphery of the lung. The majority occur close to the hilus. Pulmonary carcinoma spreads by direct extension and by lymphogenous and hematogenous metastasis. The most frequent sites of metastasis are, as is to be expected, the regional lymph nodes. In 100 per cent of the explored cases in which resection was not performed, these nodes were involved. Autopsy was performed on 41 of the 154 inoperable patients. Regional nodes were involved in every case. Next in frequency was spread, either by direct extension or metastasis, to one or both lungs. This occurred 19 times. The pleura and liver were involved 14 times each, the brain 10 times and one or more bones 9 times. These are late manifestations. Of greater practical importance are the types of spread which denoted inoperability in 154 cases at the time of diagnosis. The most frequent were: involvement of the pleura, 38 cases; supraclavicular nodes, 20 cases; recurrent laryngeal nerve paralysis, 18 cases; location of lesion at or above the main tracheal carina, 16 cases; cerebral metastasis, 11 cases; and bone metastasis, 9 cases. Phrenic nerve paralysis, direct extension to the chest wall, metastasis to the contralateral lung, to the axillary nodes, and to the liver and skin occurred with sufficient frequency to be noteworthy.

Bronchiogenic carcinoma at the University Hospital is classified into the squamous cell, the adenocarcinomatous (the gland cell type), and the undifferentiated types. The undifferentiated includes the small cell, the round cell and the oat cell types. All are graded, when possible, on a basis of 1 to 4. Although the University of Michigan Department of Pathology classifies the so-called bronchial adenomas as carcinoma, grade 1, these growths have been excluded from this study. This is in keeping with the policy of Graham<sup>2</sup> who states that his carcinoma statistics do not include adenomas unless they show definite evidence of spread. Two of the adenoma cases which had originally been classified as bronchiogenic carcinoma were thus excluded. Both had a pneumonectomy and both are living and well, one six and one five years after operation. In addition there is one case, operated on over 11 years ago, still living and well.



The squamous cell carcinoma is the most frequently found type (table 3) and it offers the best prognosis. The prognosis is poorest in the cases presenting the undifferentiated type. In the 43 cases suitable for resection, 29 or 67.4 per cent were squamous cell and of the 13 in this group still living, 8 or 61.5 per cent were of this variety.

TABLE III  
Pathological Findings According to Cell Type

	Proved Cases		Inoperable Cases		Explored No Resection		Resected	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Squamous Cell	98	42.4	53	34.4	16	47.1	29	67.4
Adenocarcinoma	45	19.5	31	20.2	4	11.8	4	9.3
Undifferentiated	81	35.1	60	38.9	11	32.3	10	23.3
Not Classified	7	3.1	7	6.5	3	8.8		
Total	231	100.0	154	100.0	34	100.0	43	100.0

Adenocarcinoma was found more frequently in women. Of the 218 proved cases in which the growth was classified, there were 28 women and 190 men. Sixteen or 57.1 per cent of the female cases had adenocarcinoma whereas only 29 or 14.7 per cent were of this type in the male group. This preponderance of adenocarcinoma in women causes one to ponder on a possible relationship between it and the so-called bronchial adenoma. Both occur more frequently in women; both are pleomorphic, sections from different portions of the same tumor often revealing different appearances; and, finally, the glandular arrangement of the epithelium seen in some adenomas has caused some pathologists to diagnose them as adenocarcinoma.

In the follow-up of the series of patients operated on there have been 17 who have died following resection, and among these there were six known and one probable recurrence. Autopsy verification was available in five of these cases. In one case the resection was for palliative reasons only, all of the growth not being removed. In examining the cause of death of these 17 patients, empyema was found to account for four or 23.4 per cent. In two of these, the empyema developed late, six and nine months respectively after pneumonectomy. It is hoped that our present use of chemotherapy and penicillin will reduce this hazard to a negligible point.

Among the living patients of the operated series, all of whom have been followed to date, only one has shown evidence of a recurrence.

### CLINICAL

Bronchiogenic carcinoma is often a relatively slowly growing tumor and the importance of early diagnosis and treatment has been stressed repeatedly. For this reason, a careful analysis was made of the time interval between the onset of the first symptoms and the diagnosis. In this connection it

must be emphasized that occasionally early symptoms are lacking or trivial and the first signs to present themselves are those of some serious metastatic lesion. Brain metastasis is a noteworthy example. Because of the frequent triviality of the initial symptoms, the patient does not seek immediate medical advice. An effort was made to determine the time between the onset of significant symptoms, and the first medical consultation. Unfortunately this information was lacking on the majority of histories, but it would appear that Overholt's <sup>7</sup> figures approximate those in this series, where this information was available. He found that in 125 cases the majority did not seek medical advice for three or more months after the onset of symptoms. For this delay the physician is not directly responsible. But he is most certainly responsible once he has been consulted. And here the figures are shocking. *In more than 50 per cent of the cases a diagnosis of bronchiogenic carcinoma was not made for six or more months after the patient sought medical advice.* Thus we find that in over half of the cases a positive diagnosis was not made until nine or more months after the onset of symptoms.

TABLE IV  
Most Frequent Initial Symptoms

Symptom	Number	Per cent
Cough	97	41.9
Pneumonia		} 160 69.2%
"Flu"	63	
Cold		
Chest Pain	48	20.7
Hemoptysis	30	12.9
Dyspnea	21	9.0
Ease of Fatigue	20	6.9

A keen awareness of the initial symptoms is important. Table 4 lists the most frequent initial symptoms and the number of times they occurred. It must be remembered that the patient may have complained of any of them alone or of a combination of two or more. The chronic cigarette cough is so prevalent today that there is a tendency to ignore it. In the 97 instances in which cough is mentioned, however, it was an initial symptom. The incidence of cough is really greater than this 41.9 per cent would indicate. Those who first complained of a cold, "flu" or pneumonia also had a cough and if these two groups were combined the incidence of cough was 69.2 per cent. In patients who have a chronic cough, any change in its character is significant. Often a dry hacking cough, the cigarette type, becomes productive and even the slightest streaking with blood should call for careful study. The development of a wheeze is important. An attack of pneumonia, "flu" or a bad cold was given by 27.3 per cent of the patients as the beginning of their illness. The acute symptoms usually responded to treatment but the patient never felt well afterwards. Hemoptysis, which here denotes any amount of blood from a slight streaking to a frank hemorrhage, was present initially in 12.9 per cent of the cases. In several instances this symptom, together with loss of weight and a confusing roentgenogram of the

chest, led to prolonged hospitalization for pulmonary tuberculosis, in spite of a persistently negative sputum, and much valuable time was lost. Cancer was not suspected and bronchoscopy was not done. Pain was a first symptom in about one-third of the cases. Chest pain should be thoroughly investigated and not dismissed with a few strips of adhesive applied to the chest. Ease of fatigue and exertional dyspnea occurred with sufficient frequency to be considered important. Loss of weight is sometimes given as the first indication that something is wrong but it is usually a late manifestation. In 16 instances the disease was ushered in with symptoms not referable to the chest. Nausea and vomiting, abdominal pain, neurological symptoms and pain elsewhere in the body are mentioned. Arthritic pain in one or more joints had been noted, the pain clearing completely following resection of the pulmonary lesion. In one case clubbing of the fingers and toes was the first thing noted.

### DIAGNOSIS

The diagnosis of pulmonary carcinoma is usually not difficult. If successful surgical removal of the lesion is to be carried out, it is essential that the patient reach the surgeon at the earliest possible time after the onset of symptoms. If the physician will but bear in mind the possibility of the existence of the disease and carefully investigate all unexplained or prolonged respiratory complaints in all persons, particularly men, past 40 years of age, many lives will be saved.

Once that cancer has been suspected and the physical examination completed, a careful fluoroscopic and roentgen-ray study should be made. At the fluoroscope one notes the presence or absence of a lesion either close to the hilus or in the periphery of the lung. Widening of the mediastinum, retraction, indicating atelectasis, and free movement or fixation of the diaphragm should be looked for. Diaphragmatic motion is important as indicating whether or not the phrenic nerve is involved by mediastinal invasion. While it is obvious that a positive diagnosis cannot be made by roentgen-ray alone, the findings, as interpreted by an expert, give a high incidence of correct diagnosis. Occasionally one may encounter an early case in which the roentgenographic findings are negative. Many bizarre findings are often encountered and it is only by wide experience and a constant *suspicion* of the condition that a proper interpretation can be made. The shadow seen may be that of the tumor itself or secondary manifestations. Tuberculosis, bronchiectasis and lung abscess offer particularly difficult differential problems at times.

Bronchoscopy is by far the most important procedure in establishing a diagnosis. Biopsy can be taken and the location and extent of the growth in the bronchus or bronchial wall can be ascertained. Occasionally a lesion, grossly carcinomatous in appearance, is seen, even though the biopsy may be reported as negative. Repeated bronchoscopies will usually result in a positive histological diagnosis. Conversely, other lesions, such as tuber-

culomas, tuberculous bronchitis, tuberculous or pyogenic granulation tissue or benign tumor, may be present and seen at the time of the bronchoscopic examination. The exact location of the growth may be of great importance in deciding on the operability of the lesion. A lesion too close to, or involving the main carina, or one extending too far up along the lateral wall into the trachea, is obviously not removable. A positive bronchoscopic biopsy is, of course, dependent on the lesion's being located in one of the accessible bronchi or growing out of one of the primary or secondary branches. In the present series bronchoscopy was performed in all 77 of the operable cases and in 112 of the 154 inoperable group. Patients who were too ill or in whom there were obvious metastatic lesions, were not subjected to the procedure as the result would have been of academic interest only. Tissue for histological examination was obtained in 19 or 81.2 per cent of the inoperable group and in 47 or 61 per cent of those on whom operation was performed. However, the percentage of positive biopsies was nearly the same in the two groups, being 90.1 per cent and 86.3 per cent, respectively.

Bronchography is useful at times in that it may indicate an obstructed bronchus beyond the field of bronchoscopic vision. In certain cases this may be of definite value in the differential diagnosis.

Punch or aspiration biopsy was used four times in this series but it is a potentially dangerous procedure and is not recommended.

The presence of pleural fluid does not necessarily mean pleural metastasis but the finding of bloody pleural fluid is generally considered an indication of neoplastic involvement denoting inoperability. The finding of carcinoma cells in the pleural fluid establishes the diagnosis. They were found in seven of the 38 cases with pleural fluid. None of the 38 cases was operable. Neoplastic cells may occasionally be found in the sputum.

Finally if all other means fail to establish a positive diagnosis and roentgenological evidence is sufficiently strong, there being no obvious metastatic lesions or other contraindications, exploratory thoracotomy should be done. It is a relatively safe procedure and carries a low mortality and morbidity rate. The average stay in the hospital is less than two weeks, comparable to exploratory laparotomy. Direct examination by both palpation and inspection is possible and tissue can be removed for frozen section diagnosis if necessary. *Since early resection is the only hope of cure the slight risk of the thoracotomy is not to be compared with the hazard of waiting for a positive diagnosis which may only come in the form of a hopeless metastatic lesion.*

#### TREATMENT

There is, at the present time, a complete unanimity of opinion that the only curative treatment of bronchiogenic carcinoma is complete removal of the cancerous tissue, together with all involved or suspicious mediastinal lymph nodes. Total pneumonectomy rather than lobectomy is usually recommended as it is the best means whereby one can be assured of remov-

ing all regional nodes. Usually there is no choice as in the majority of cases the location of the bronchial lesion demands it. Occasionally emphysema in the contralateral lung and dyspnea make a lobectomy advisable, if it is technically possible. In such cases the risk of recurrence is probably not as great as the possibility of having a respiratory cripple as the end result. Ordinarily the remaining lung shows a great capacity for the necessary compensatory changes and only one patient in the living group is suffering from more or less disabling dyspnea. Lobectomy has been performed on four patients in this series of cases.

Roentgen-ray therapy, except for palliative reasons in the inoperable or non-resectable cases, is mentioned only to be condemned. It does not cure and the feeling of well being and improvement following its use usually causes the patient to postpone a possible curative operation until the lesion has reached a prohibitive stage.

Present day operative mortality is relatively low, 5 to 20 per cent, and the final results of this and other reported series of cases attest to the value of pneumonectomy for an otherwise 100 per cent fatal disease. Seventeen patients or 39.5 per cent lived for from two months to three and a half years. Thirteen patients or 30.2 per cent are alive from two years to seven years post-operatively. All are in good health except one of the lobectomy patients who has had a recurrence.

The true value of any surgical procedure is not reflected in, and should not be judged by, the immediate operative mortality. A very low early and late surgical mortality rate can be obtained by accepting for resection only those patients who have early lesions and who are in good condition, thus condemning to certain death many who might otherwise be cured. To quote Graham,<sup>6</sup> speaking of the dilemma of the thoracic surgeon, "Shall we offer a chance to the bad risk victim of bronchiogenic carcinoma, even if it is only a small one, to be cured of his otherwise hopeless condition, or shall we decline to operate because of the great danger of an operative mortality?"

#### SUMMARY AND CONCLUSIONS

A careful analysis of 231 proved cases of bronchiogenic carcinoma is presented. Only 77 of this group were considered operable and in only 43 of these 77 was resection possible. Seventeen or 39.5 per cent of the resected cases lived for from two months to three years post-operatively and 13 or 30 per cent are alive from two to seven years after operation.

The majority of patients do not seek medical aid for three or more months after the onset of symptoms and in over 50 per cent of the cases there is a delay of six or more months in establishing the diagnosis. Until the avoidable delays in diagnosis are overcome there can be little chance of increasing the present relatively small number of possible cures of lung cancer. The optimum time of operation is within six months of the onset of significant symptoms. This does not mean that it is safe to delay opera-

tion for as long as six months. Operation should be performed *as soon as* a tentative or actual diagnosis can be made. Routine chest roentgen-rays are essential to an early diagnosis of the peripheral type of lesion which usually presents no early symptoms. The squamous cell type offers the best prognosis.

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# REHABILITATION: WARTIME LESSONS APPLIED TO PEACETIME NEEDS \*

By HOWARD A. RUSK, M.D., F.A.C.P., *New York, N. Y.*

THE service convalescent training program was born of necessity. With a general shortage of time and men in the early days of 1942, it was not feasible to wait for leisurely indolent convalescence and the time necessary for nature to take its course. The original program was started at Jefferson Barracks, Missouri in November 1942 after the great need was emphasized by Brigadier General Hugh Morgan on one of his early inspection trips.

Designed originally for the pre-combat sick or injured soldier, the program had a dual mission: first, to send the soldier-patient back to duty in the best possible physical condition in the shortest possible time; second, to teach the soldier-patient something that would make him a more efficient and more effective fighting man. With the inception of this program, physical activity and military education became as much a doctor's prescription as drugs and diet. The results achieved proved so successful in the experimental phase of the program that in December, 1942 such a program was initiated in all Army Air Forces hospitals.

The classroom and gymnasium were moved into the wards for it was noted early in the convalescent program that to obtain maximum results, reconditioning should start as early as possible following acute disease or injury, and the program had to be purposeful, progressive, and graduated to the individual patient's physical tolerance.

In order to make the soldier-patient a member of the therapeutic team, the HANDBOOK OF RECOVERY (AF Manual No. 23) <sup>1</sup> was prepared as a prescription blank for all types of orthopedic disabilities. It included a nine-page section on anatomy, physiology and pathology written in simple language to show the soldier-patient why he was in the program, the value and effects of active exercise, how bones, muscles and nerves are made, what happens when they are injured and how they heal. This was followed by a series of two-page prescription blanks for the specific injury demonstrating to the soldier-patient by diagram the normal function of the injured part, his diagnosis and disability, the type of physio-therapy necessary, the illustrated active exercises to be done with and without supervision, and a personal objective recovery chart which the patient himself maintained. This was an effective innovation as it not only gave the patient an insight into and understanding of his condition, but great motivation through his ability to measure his own progress objectively.

LET'S WALK (AF Manual No. 49) <sup>2</sup> was another publication designed for the patient which met with widespread use and approval. Unique in its

\* Address delivered at the Twenty-Seventh Annual Session of The American College of Physicians, Philadelphia, May 15, 1946.

presentation, this booklet dealt with the functional aspects of walking with the use of aids. It first gave the patient a brief psychological orientation to his disability and then proceeded to demonstrate objectively through the use of illustrations and charts the factors involved in walking with aids.

Some of the pertinent observations made on the results of the Convalescent Training Program after three years of experience were: hospitalization time was shortened; hospital readmissions were reduced; sick leaves were eliminated except in extraordinary cases; and the morale of the soldier-patients was immeasurably improved when they were kept busy and interested in purposeful activity.

A number of interesting clinical studies were made. Van Ravenswaay<sup>3</sup> and his co-workers studied 645 cases of virus pneumonia treated in the same acute ward. These cases were later assigned to alternate convalescent wards. In Ward I "nature was allowed to take its course" and men sat around until they and the medical officer felt they were ready for duty. In Ward II the patients were kept in bed until their sedimentation rate reached 10 mm. in one half-hour and then were put in a reconditioning program, beginning with exercise for one-half hour the first day and increasing progressively until the twelfth day when the patient was participating in a full five-hour day of physical training, mass games, competitive sports and active recreation including a ten mile hike. Group I averaged 45 days' hospitalization with a 30 per cent recurrence rate. The patients in Group II averaged only 31 days with but a 3 per cent recurrence rate.

Karpovich<sup>4</sup> and his associates at the School of Aviation Medicine, San Antonio, Texas, studied a similar group of 200 aviation cadets convalescing from virus pneumonia. Using a modification of the Harvard Step Test and starting as early as the first afebrile day, Karpovich found that by the reactions to this test it was possible to determine, with some degree of accuracy, the patient's ability to enter into and participate in an active convalescent program. An interesting by-product of Karpovich's work was the observation that patients undergoing the tests required five days less hospitalization time than those participating in the general program. These findings were suggestive of the ability of the convalescent to participate in an even more active program with beneficial results.

Early in the operation of the convalescent program it was noted clinically that orthopedic patients requiring fixation of a specific member did not, if kept in top physical condition generally, show the usual degree of muscular atrophy in the fixed part and when the cast was removed could be reconditioned to duty in approximately one-half the usual convalescent time. Whether this was due to increased blood velocity, exercise within the cast, vasomotor stimulation, or lack of capillary loss gives food for thought and further investigation.

As a part of the AAF Rheumatic Fever Control Program, Karpovich, Weiss, Starr and Ershler<sup>5</sup> carried out a study on physical fitness testing and physical training of convalescent rheumatic fever patients. Because of the



chronic, recurrent nature of the disease and the possibility of disabling cardiac sequelae, it was felt that special emphasis should be placed on the standardization of physical activity and convalescent training of these patients by working out a series of graduated physical fitness tests which could be used, in conjunction with the usual clinical observations, to determine the rate at which the patient could safely be permitted to progress to increased physical activity. The details of this study are available in the original report. It is interesting to note, however, that there were no recurrences or untoward reactions in any patient participating in the study.

Reports on the effects of bed rest have been detailed in the literature,<sup>6, 7, 8, 9</sup> and special studies have been made by Keys<sup>10</sup> and Barr<sup>11</sup> and his associates. Reports on the effects of early ambulation in surgical patients have been made by Powers<sup>12</sup> and Whipple,<sup>13</sup> and their significant observations are most pertinent in evaluating the management of convalescence.

To meet the needs of overseas combat casualties special convalescent hospitals were activated in 1943. These hospitals were designed to meet the needs of the whole man regardless of what those needs were—medical, physical, psychiatric, social, vocational, educational or personal. The physical reconditioning program emphasized competitive team play and active recreation. The educational program consisted of training in military specialties. This combined emphasis on both physical and educational training provided the diversional media through which, with the aid of personal counseling and psychological readjustment, resocialization of the individual patient was achieved. The purpose of the program was to provide the soldier-patient with a laboratory of opportunity through physical reconditioning, educational-avocational pursuits and recreation whereby he might recover the attitudes, habits, and values compatible with normal behavior patterns.

In the convalescent hospital each patient was assigned to a designated "personal physician." This personal physician was carefully chosen because of his training, experience and ability to understand and evaluate the problems of the patient. Many physicians were given special clinical courses in the newer psychiatric, diagnostic, and therapeutic technics. They were in reality specialists in the psychology of emotional stress and the sciences of organic repair.

After a thorough evaluation of a patient's disability, the personal physician was ready to turn to the team of ancillary specialists for specific corrective measures in the fields of physical, medical, educational, occupational and recreational therapy. He served as a coördinator in integrating the work of these specialists in their coöperative efforts toward restoration of the normal physical and functional being of the whole man.

The rehabilitation programs of the armed forces have demonstrated what can be done for the physically and emotionally wounded and handicapped to make them self-sufficient, self-respecting, self-supporting persons.

Both the medical profession and the general public are genuinely con-

cerned with the problem which must be faced by thousands of our disabled veterans as they return to their communities. These men have earned and deserve the best that a grateful nation can give them, but few of us realize that in comparison to the total numbers, our disabled veterans constitute only a small part of the handicapped and disabled we have in this country.

We had in 1940 in the United States some six and one-half million disabled males between the ages of 15 and 64 years, men who normally would be income-producing. These six and a half million, plus the number of disabled or handicapped veterans being discharged from our military hospitals will give us, when demobilization is completed, approximately eight million working age males who are disabled to the extent of requiring physical or vocational rehabilitation or special placement aids, if they are to be successfully employed. This represents one person in sixteen in our general population, and one in seven in our male working population. The number of persons who are permanently disabled by accident alone increases by 350,000 each year. The total problem has been summarized by Donahue and Tibbitts.<sup>14</sup>

During the first four years of war there were approximately 17,000 amputations in the Army, but during this same period there were 120,000 major amputations necessitated by disease or accident in our civilian population.

The armed forces and some outstanding community and civilian agencies, such as New York's Institute for the Crippled and Disabled, have demonstrated that the physical and emotional rehabilitation of our handicapped and disabled is possible. Some authorities have estimated that up to 97 per cent of all our handicapped can be rehabilitated to such an extent that they can be gainfully employed.

The short labor market during the war gave many disabled persons the first opportunity of their lives to take a place on the production line and prove that they could, with good selective placement, produce on a par with the normal workers. An example is the Ford Motor Company River Rouge plant where more than 11,000 handicapped civilian workers were employed.

During the war 83 per cent of our nation's industries employed handicapped workers. Those industries have reported that among the handicapped there has been a much smaller labor turnover, less absenteeism, fewer accidents and equal or higher production rates. Many employers before this vast experience with handicapped employees, had a fear of increased accident rates. The industrial accident rate of 87 of the great industrial plants in America, each having from 200 to 12,000 handicapped employees, has disproved that conception.

The answer to the utilization of handicapped workers lies not so much in "fitting the job to the worker" as in "fitting the worker to the job." Through this procedure the worker in reality becomes non-handicapped as far as his particular job is concerned.

Most individuals use less than 10 per cent of their potential efficiencies in

normal pursuits. It is only in emergencies that we called upon our tremendous reserves of physical power and ability. In many cases a worker's physical defect acts as a tremendous stimulus to over-compensation, resulting in extraordinary physical ability. Adler<sup>15</sup> developed a complete system of psychology on the basis of inferiority. The employer of handicapped workmen is putting that psychology into purposeful and gainful application.

The National Office of Vocational Rehabilitation has reported how rehabilitation pays off economically.<sup>16</sup> Of the 43,997 persons undergoing vocational rehabilitation under this agency in 1944, 22 per cent or more than 10,000, had never been gainfully employed. The average annual wage of the entire group prior to rehabilitation was \$148. After rehabilitation, the average annual wage of the group increased to \$1,768. The total earnings of the entire group rose from \$6,510,556 to \$77,786,696.

Prior to rehabilitation the majority of these persons relied on general public assistance. The annual cost of this assistance to the taxpayer was from \$300 to \$500 per case, but the total cost of their rehabilitation averaged only \$300 per case, a non-recurring expenditure.

No degree of economic gain, however, can measure the social and moral satisfactions obtained by the successfully rehabilitated and employed handicapped worker and his family. Nor can it measure the value to society in the transformation of these individuals from dependents to productive, self-reliant individuals.

The question usually raised is, "If the vocational rehabilitation program has been so successful, why isn't it extended to meet the needs of the entire nation?" The answer is simply that the rehabilitation centers to which these cases can be referred do not exist. The funds and authority are available, but the facilities for doing the job are inadequate. Several national organizations are making efforts to stimulate public interest in rehabilitation by demonstrating to both the medical profession and the public what actually can be done by an integrated rehabilitation program.

The Baruch Committee on Physical Medicine has recently published a report<sup>17</sup> translating the experience of the armed forces into civilian application in order that this experience may be made available to the medical profession and those interested in community rehabilitation centers. They are blueprinting a model center, outlining its mission, organization, components, physical set-up, approximate cost, and its relationship to the medical and allied professions—industry, labor, social, and governmental agencies—and to the community as a whole.

Rehabilitation is primarily a medical problem and our responsibility does not end when the discharge note is made on the hospital chart. Disease cannot be divorced from the problems of personality, economy, and social adjustment.

The retraining of the paraplegic and the hemiplegic is just as important as the medical management. The cardiac and the arthritic often need vocational or avocational readjustment just as badly as they need medication.

The attitudes of the chronic invalid can change entirely with the simplest routine of productive activity.

Utilizing the experience of the armed forces, civilian hospitals can be made into institutions of opportunity. Surveys have shown that the average patient in the hospital spends 10 per cent of his time in pain and 90 per cent in boredom. There is real need for dynamic hospital programs designed to aid the convalescent patient in his orientation back to normal living. Classes in dietetics, pre-natal care, home nursing, consumer buying, and home economics can be combined with forum discussion groups, craft courses designed especially for the homebound, and programs which are aimed to promote a better understanding of our new responsibility as citizens in a global world. Special training films on various industrial projects, travel, vocational information, and films of historical and scientific interest are available without cost from numerous sources. With such a convalescent program this phase of hospitalization could be transformed from one of boredom to one of opportunity.

A recent survey made in a large general hospital revealed that 5 per cent of the general surgical patients, 15 per cent of the medical patients and 85 per cent of the orthopedic patients were in need of no further definitive care but were in need of rehabilitation and retraining in order to go back to work. Thirty per cent of all patients visiting the medical and surgical out-patient clinic were in the same category. Thousands of critically needed hospital beds could be made available, with great advantage to the patient, if rehabilitation and convalescent facilities were available.

Specialized rehabilitation centers must be established to serve the severely handicapped, to furnish the third phase of medical care that takes the patient from the bed back to productivity. This is a medical responsibility—a medical necessity—if we are to fill the existing gap in the complete care of the patient.

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# PENICILLIN IN THE TREATMENT OF NEUROSYPHILIS. IV. CEREBROSPINAL FLUID CHANGES IN CASES OF SYMPTOMATIC NEUROSYPHILIS \*

By FRANK W. REYNOLDS, M.D., *Baltimore, Maryland*

A STUDY of the effect of penicillin in various forms of neurosyphilis was begun at the Johns Hopkins Hospital in October 1943. The results of the first two years' experience are being reported in a series of papers. The first of these <sup>1</sup> dealt with the treatment of asymptomatic neurosyphilis, the second <sup>2</sup> with general paresis, and the third <sup>3</sup> with Erb's spastic paraplegia. The present paper, the fourth of the series, is concerned with the changes in the cerebrospinal fluid abnormalities in various types of symptomatic neurosyphilis considered as an admittedly conglomerate whole.

Although there are disadvantages in grouping together such widely divergent entities as general paresis, tabes dorsalis, meningovascular neurosyphilis and Erb's spastic paraplegia, the amalgamation is justified by the fact that all have in common *T. pallidum* as the causative agent and specific abnormalities in the cerebrospinal fluid.

The clinical evaluation of the results of therapy in cases of neurosyphilis is subject to two difficulties: (1) clinicians vary in their backgrounds, in their special interests and in their interpretations not only of subjective but also of objective phenomena; and (2) because neural tissues, once destroyed, do not regenerate, it is not infrequently debatable what proportion of residual neurologic or psychiatric abnormalities is due to treatment failure and what proportion is due to irrevocable pre-treatment tissue destruction. These are considerations which make it a matter of extraordinary difficulty to evaluate clinical results of treatment.

The spinal fluid abnormalities are, on the other hand, objective and unequivocal criteria which may be analyzed quantitatively without qualification of the raw data.

These considerations have led such a careful neuropsychiatric observer as Dattner <sup>4</sup> to the opinion that the efficacy of any form of treatment in neurosyphilis should be determined by the response of the cerebrospinal fluid and not by clinical data.

## CASE MATERIAL

As of January 1946, 149 patients with various clinical manifestations of neurosyphilis have been treated with penicillin. Forty-one of these patients

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had general paresis; 13 were considered to have taboparesis; 45 had either tabes dorsalis, primary optic atrophy, or both; 19, meningovascular neurosyphilis; six, Erb's syphilitic spastic paraplegia; and 25 patients herein "unclassified" had in most instances pupillary abnormalities only.

One hundred and eleven of these patients were treated with penicillin alone, in amounts ranging from 2.0 to 10.0 million units in divided doses; the remaining 38 patients received from 2.0 to 6.0 million units of penicillin in divided doses concurrently with induced tertian or quartan malaria.

The sodium salt of commercial penicillin was used throughout. The preparations used were those of several manufacturers and of many lot numbers. The composition in terms of the now identified penicillin fractions,

TABLE I

Summary of Case Material: Diagnosis, Race, Sex, and Age, and Cerebrospinal Fluid Grouping in Terms of Degree of Abnormality

Diagnosis	Cases	Race and Sex				Age								CSF Group			
		W.M.	W.F.	C.M.	C.F.	10-19	20-29	30-39	40-49	50-59	60-69	70-79	Normal	1	11	111	
Tabes Dorsalis and Primary Optic Atrophy	45	20	8	16	1	1	2	15	19	4	1	3	2	0	16	27	
General Paresis	41	23	6	11	1	1	5	12	15	3	5	0	0	0	0	41	
Tabo-Paresis	13	8	2	3	0	1	0	4	6	2	0	0	0	0	2	11	
Meningovascular Neurosyphilis	19	4	2	10	3	0	3	9	7	0	0	0	0	0	2	17	
Erb's Spastic Paraplegia	6	3	1	2	0	0	0	1	3	1	1	0	0	0	3	3	
Unclassified Neurosyphilis	25	5	2	9	9	1	4	9	9	2	0	0	1	0	6	18	
		63	21	51	14	4	14	50	59	12	7	3	3	0	29	117	
Totals	149	84		65													
		149				149								149			

G, F, X, and K, is unknown. Aqueous solutions were injected intramuscularly every three hours, day and night. Individual doses ranged from 40,000 to 50,000 units; the total number of injections, from 50 to 200. Intrathecal therapy was not employed. Those treated with malaria inoculata were allowed to have from eight to 12 paroxysms, and approximately 40 hours of fever in excess of 104° F. Penicillin was usually begun at the time of the first apparent malarial fever.

A summary of the case material upon which this study is based is given in tables 1 and 2. Included in the group were 114 male and 35 female

TABLE II  
Summary of Case Material: Diagnosis, Penicillin Plus Malaria vs. Penicillin Alone, Penicillin Dosage, Duration of Symptoms, and Cumulative Duration of Follow-Up Observation

Diagnosis	Cases	Duration of Symptoms (in months)					Peni- cillin plus Ma- laria	Penicillin Dosage (in millions of units)	Cumulative Duration of Follow-Up Observation (in weeks)												
		Less than 6	6- 12	12- 24	More than 24	Un- known			Less than 4.0	4.0- 8.0	More than 8.0	0	1- 4	10- 19	20- 29	30- 39	40- 49	50- 59	60- 79	80- 99	100- 120
Tabes Dorsalis and Primary Optic Atrophy	45	9	9	2	11	14	13	32	8	19	5	45	42	34	32	29	25	20	12	4	0
General Paresis	41	16	9	8	7	1	17	24	2	13	9	41	40	37	26	17	11	8	5	4	4
Tabo-Paresis	13	2	4	1	6	0	7	6	5	1	0	13	13	12	12	10	8	7	5	5	2
Meningovascular Neuro- syphilis	19	9	4	0	4	2	1	18	1	17	0	19	19	18	12	11	10	9	8	0	0
Erb's Spastic Paraplegia	6	2	0	1	3	0	0	6	2	2	2	6	6	5	4	3	1	1	1	1	0
Unclassified Neurosyphilis	25	0	0	0	3	22	0	25	2	23	0	25	25	23	15	14	13	10	6	2	1
Totals	149	38	26	12	34	39	38	111	20	75	16	149	145	129	101	84	68	55	37	16	7



patients; 84 whites and 65 Negroes. The mean age of these patients was 43.6 years, the youngest being 10, the eldest 79 years.

Using Moore's<sup>6</sup> classification, by far the greatest number of pretreatment spinal fluids were Group III, with increased cell count, elevated spinal fluid protein, strongly positive Wassermann reactions, and "first zone" colloidal mastic tests. Twenty-nine spinal fluids were classified as Group II, or intermediate in degree of abnormality; none as Group I. Three spinal fluids were normal at the time treatment was instituted.

Thirty-six patients (24 per cent) had had a recent onset of symptoms, i.e., less than six months. In 64 (43 per cent), the first symptoms had been present for less than one year prior to admission. The duration of symptoms was unknown in 39 cases, including almost the entire group of patients with "unclassified" neurosyphilis.

Seventy-one had received some previous antisyphilitic therapy: 11 malaria plus chemotherapy, 60 varying amounts of arsenical and bismuth chemotherapy alone. In no case had malarial therapy been given within a year prior to the institution of penicillin therapy. In only seven of the patients previously treated had any improvement been apparent; all of these but two having received malaria. No patient markedly improved from any previous treatment was treated with penicillin.

#### EFFECTS OF THERAPY

The overall effect of treatment upon the spinal fluid abnormalities (cell count, total proteins, colloidal mastic, Wassermann reactions) is shown in figure 1.

*Cell Count and Total Proteins:* Following treatment with penicillin alone or with penicillin plus malaria, the pleocytosis of the cerebrospinal fluid almost invariably became normal. This was a prompt, and during the period of observation, generally a well-sustained effect.

A similarly favorable and almost as prompt effect upon the total proteins of the cerebrospinal fluid was apparent.

Applying the Dattner-Thomas<sup>4</sup> concept of "activity," as judged by increased cell counts and total proteins, there were nine patients with evidence of an "active" process in the central nervous system six or more months after treatment. Of these, three had general paresis, one tabes, two taboparesis, one Erb's spastic paraplegia and two unclassified neurosyphilis. Since 96 patients have been under observation for six or more months, 9 per cent of those followed for that length of time had evidence of activity six months or more later. One of these is known to have become normal subsequently without further antisyphilitic therapy.

*Colloidal Mastic Test:* In analyzing the results of treatment upon abnormalities in the colloidal mastic test, an artificial statistical device has been utilized. The arithmetic sum of the arbitrarily assigned readings of the first three tubes was used. Thus, a colloidal mastic of 554321000 would be recorded as 14, and one of 22111000000, as 5.

It is evident from figure 1 that penicillin therapy favorably influences the results of the colloidal mastic test. It also is apparent that this effect, while neither as prompt nor, during the observation period, as complete as in the case of the cell count and total protein, was similarly well sustained. There was no case followed for more than one year in which some improvement in the results of this test had not occurred.

*Spinal Fluid Wassermann Test:* The statistical concept of reciprocal relationship was utilized in analyzing the effects of therapy upon the cerebrospinal fluid Wassermann titer. In our laboratory, the spinal fluid

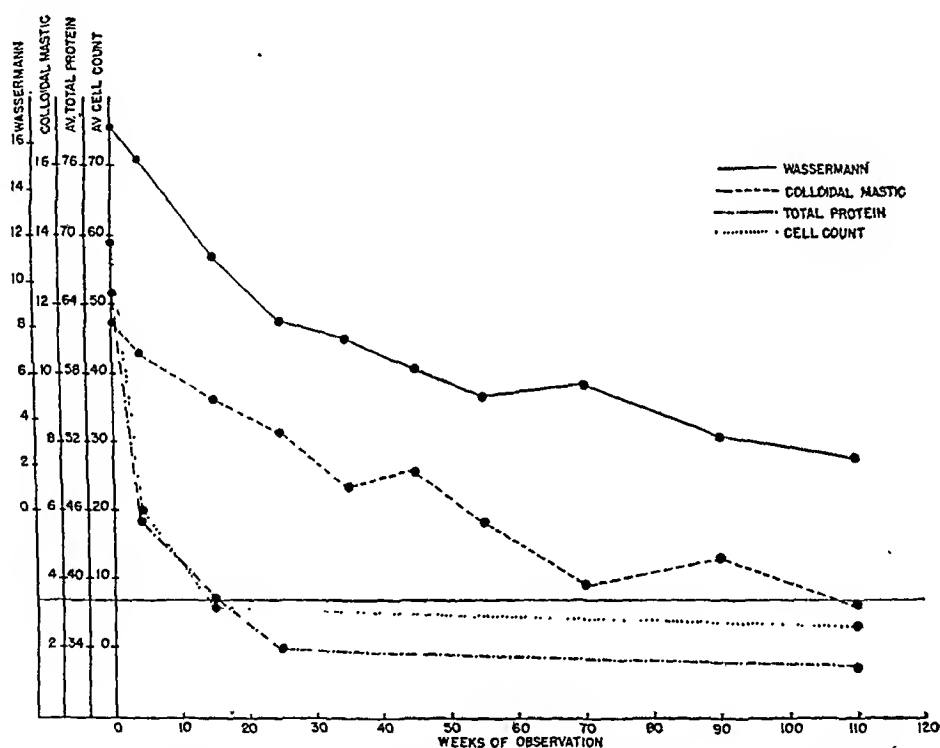


FIG. 1. Changes in fluid abnormalities following treatment with penicillin or penicillin plus malaria.

Wassermann is quantitated by the use of decreasing amounts (1.0, 0.8, 0.6, 0.4, 0.2, 0.1, 0.05, 0.03 and 0.01 c.c.) of spinal fluid, and the result recorded as the minimal quantity necessary for complete fixation of complement. The following arbitrary reciprocal values were assigned to the several readings: 0.01-100; 0.03-33; 0.05-20; 0.1-10; 0.2-5; 0.4-2.5; 0.6-1.6; 0.8-1.2; 1.0-1.0; negative -0. The mean of the reciprocal is the basis for the graphic analyses of this paper.

Therapy with penicillin or with penicillin plus malaria was found to lower gradually the average Wassermann titer of the cerebrospinal fluid of this group of patients with asymptomatic neurosyphilis.

The favorable effect, perhaps even more than that noted upon the results of the colloidal mastic test, was of slow evolution. It was, however, equally

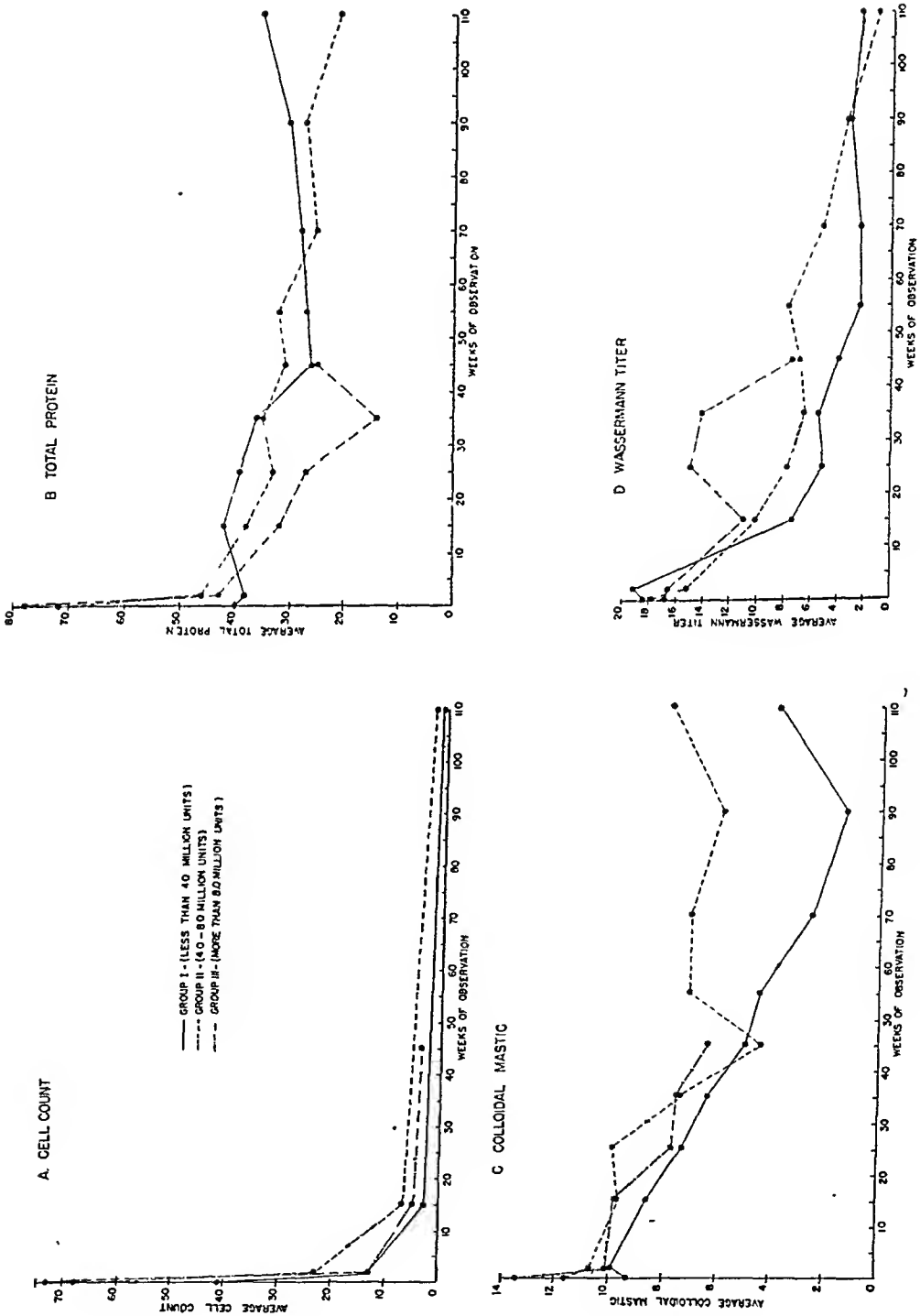


FIG. 2. Effect of penicillin dosage (penicillin alone).

well sustained. All but five (of 53) patients (two with tabes, three with unclassified neurosyphilis) who were followed for one year or more, have shown some decrease in the spinal fluid Wassermann titer.

### FACTORS INFLUENCING THE RESULTS OF TREATMENT

1. *Penicillin Dosage*: The optimal dosage of penicillin in the treatment of neurosyphilis is not known. None of the patients in this study received more than 10 million units. In evaluating the effect of penicillin dosage, only those 111 patients treated with penicillin alone were considered.

A comparison of the results of treatment with less than 4.0 million units (Group I), 4.0 to 8.0 million units (Group II) and with more than 8.0 million units (Group III) is shown graphically in figure 2. Analysis of these data shows no distinct advantage in the use of larger doses. In the light of recent information<sup>6</sup> which indicates that the composition of commercial penicillin was changing during the period of this study, no conclusions can be drawn from this observation.

2. *Duration of Symptoms*: In the second paper of this series, it was pointed out that although in patients with general paresis there was no significant effect of the duration of symptoms upon the response of the spinal fluid cell count, total proteins or colloidal mastic test, the spinal fluid Wassermann did become less strongly positive, more rapidly and to a more significant degree, among patients whose symptoms were of less than one year's duration.

When all cases of neurosyphilis are considered as a single conglomerate group, no significant effect of duration of symptoms upon any of the spinal fluid abnormalities, including the Wassermann, can be demonstrated (figure 3).

3. *Extent of the Cerebrospinal Fluid Abnormalities*: Although the vast majority (117 of 149) of the initial spinal fluid examinations in this group of patients are classified as Group III (Moore), it seems desirable to ascertain whether the extent of the cerebrospinal fluid abnormalities at the time treatment was started influences the response to therapy.

The data shown in figure 4 indicate that the spinal fluid changes approach normality at about the same rate no matter how extensive they may have been at the time therapy was instituted. Lesser degrees of adventitiousness fade into the normal range in a shorter period of time than do those more extensive, but apparently only because the initial degree of severity was less removed from the norm.

4. *Penicillin Alone vs. Penicillin plus Malaria*: In general, it may be stated that the spinal fluid response to therapy was more striking in the group of patients treated with concurrently administered penicillin-malaria treatment than among those treated with penicillin alone.

Study of figure 5 reveals little difference between the two groups in respect to the immediate effects upon the cell count or total proteins. In

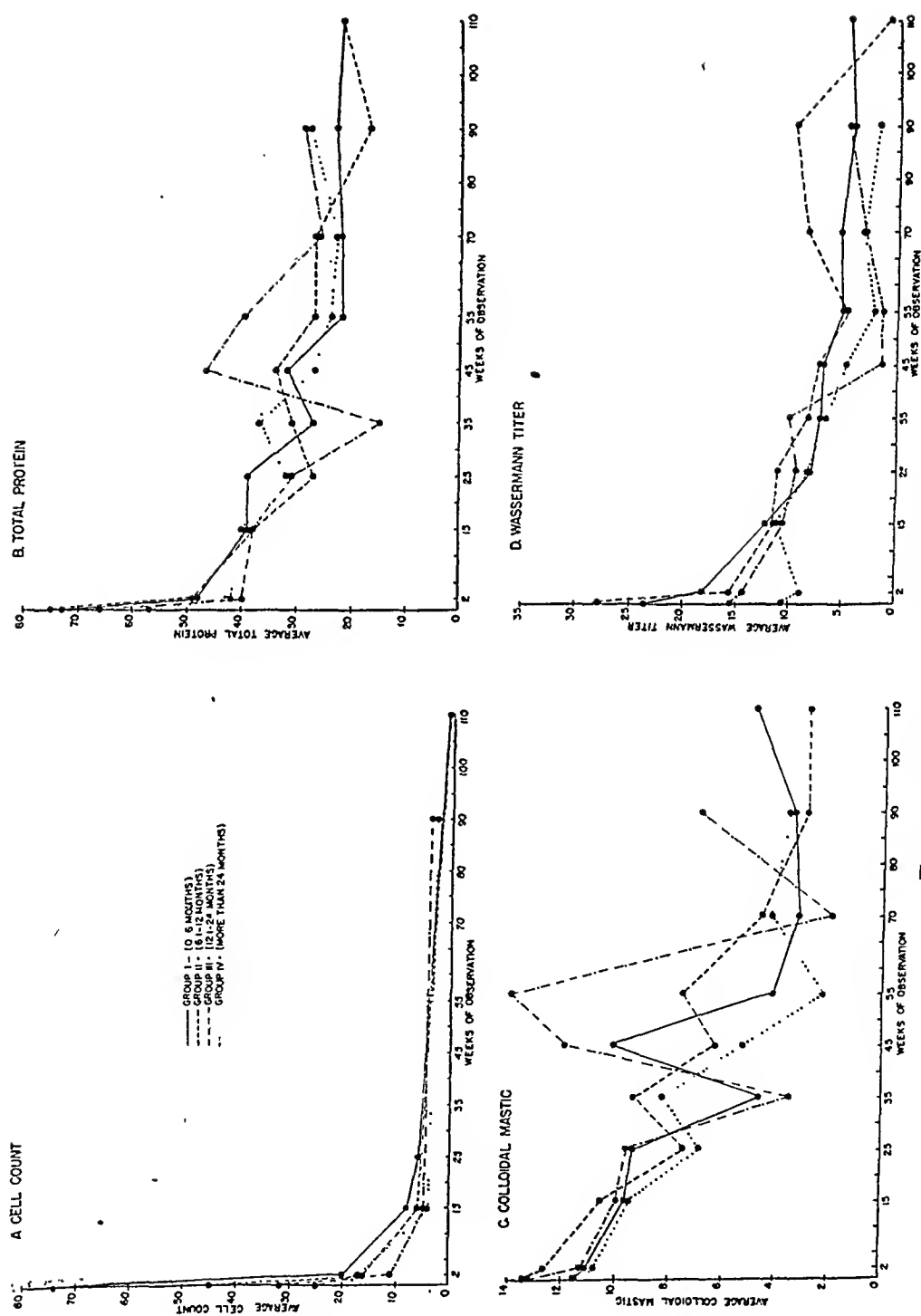


FIG. 3. Effect of duration of symptoms.

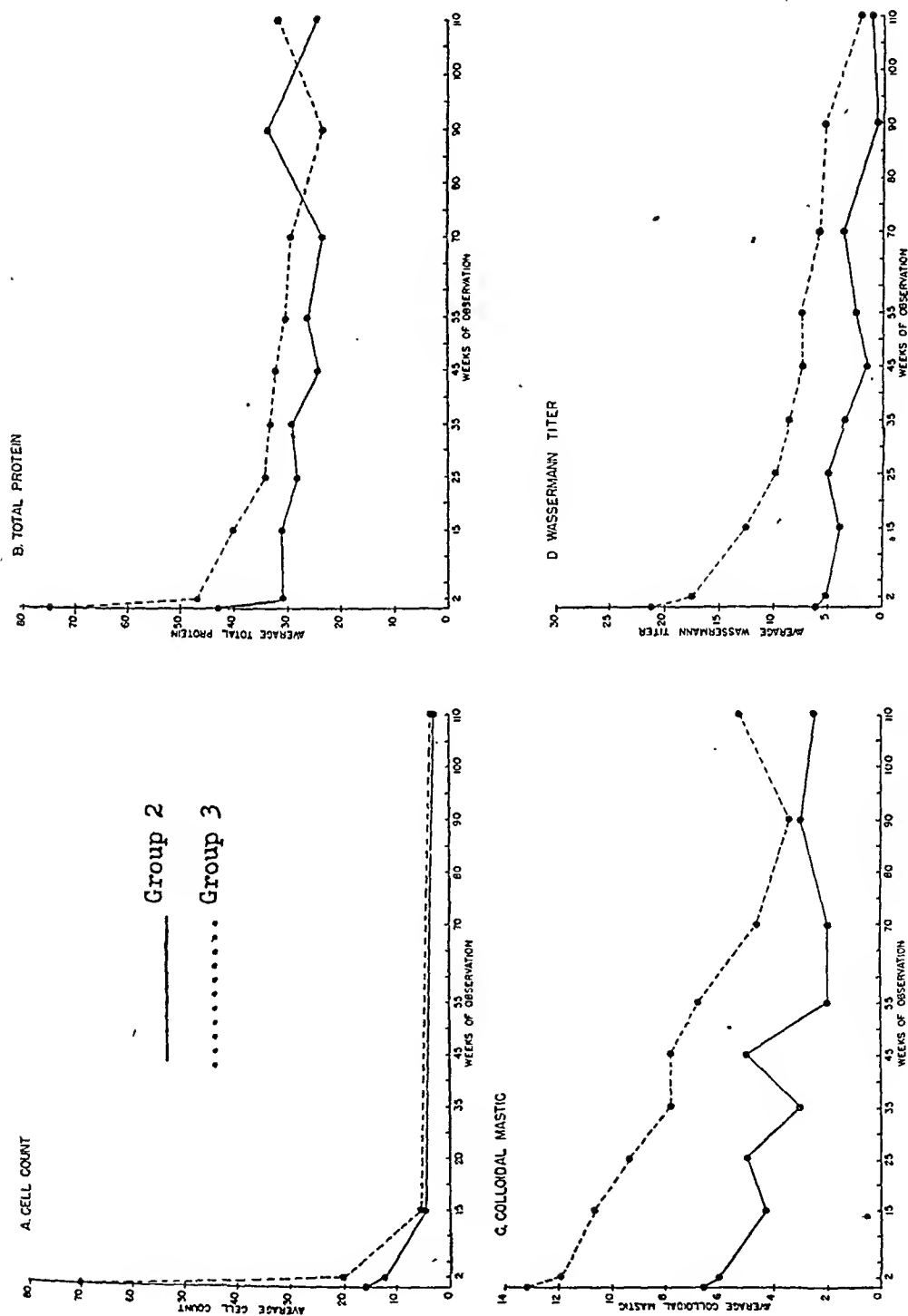


FIG. 4. Effect of cerebrospinal fluid groups.

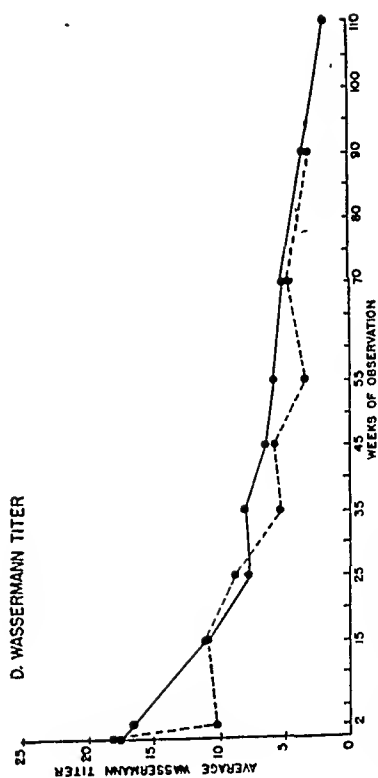
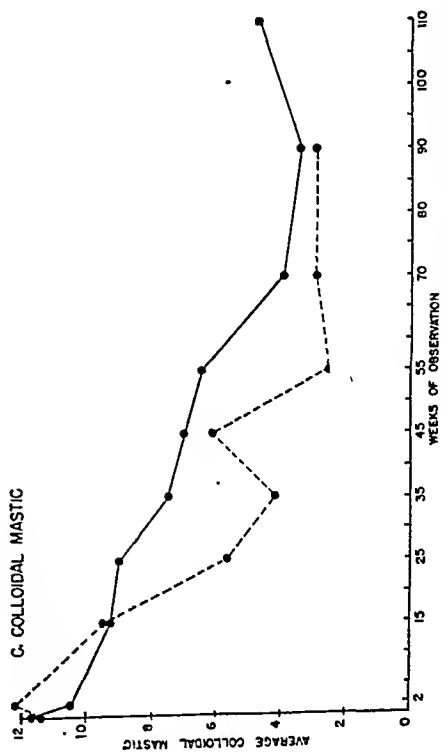
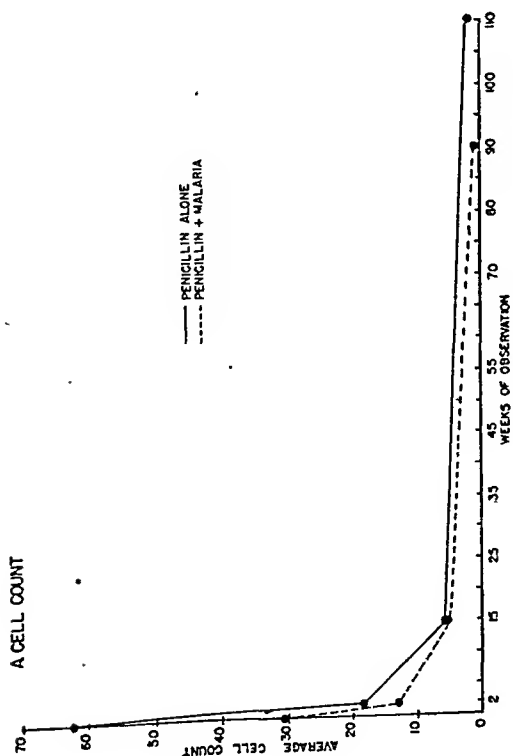
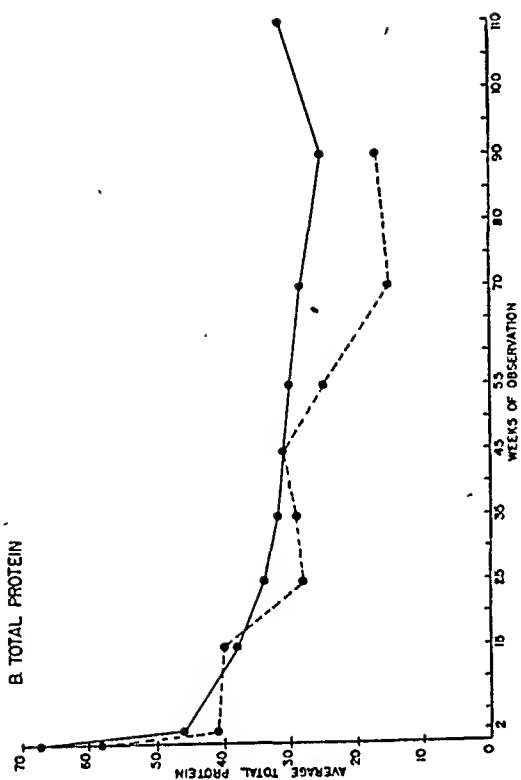


Fig. 5. Penicillin alone vs. penicillin plus malaria.

both groups, the response was prompt, almost invariably complete and generally well sustained.

Considering the colloidal mastic test and the Wassermann titer in the cerebrospinal fluid, there appears to be some evidence at least that concurrent penicillin-malaria is superior to penicillin alone.

### DISCUSSION

Although there are definite disadvantages in considering as one the several forms of neurosyphilis, varying as widely as acute meningovascular syphilis and chronic Erb's spastic paraplegia, we have sought thereby to arrive at some conclusions as to the overall effect of penicillin upon the spinal fluid of patients with neurosyphilis.

Many important questions cannot be answered fully as yet: the precise mode of action of penicillin in syphilis of the central nervous system; the optimal time-dose relationship; whether penicillin ultimately will replace entirely malarial therapy; and perhaps most important of all, the ultimate outcome for these patients in terms of years of observation. However, the improvements noted in the various cerebrospinal fluid abnormalities indicate, and clearly, we believe, that penicillin is a valuable addition to the therapeutic armamentarium in the management of patients with neurosyphilis.

### SUMMARY

1. One hundred and forty-nine patients with various clinical manifestations of central nervous system syphilis have been treated with penicillin. Of these, 111 received penicillin alone, and 38 penicillin concomitantly with malarial therapy.

2. Improvement in the spinal fluid abnormalities generally was apparent. As a rule, the cell count and total proteins promptly became and remained normal. Colloidal mastic and Wassermann tests gradually improved, the improvement being well-sustained.

3. The degree and rapidity of improvement could not definitely be correlated with (a) the penicillin dosage; (b) the duration of symptoms; nor (c) the extent of the spinal fluid abnormalities.

4. More favorable results followed therapy with penicillin plus malaria than treatment with penicillin alone.

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# THE MANAGEMENT OF INFECTIOUS HEPATITIS \*

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## INTRODUCTION

DURING the last five years the incidence of infectious hepatitis has approached epidemic proportions among both civilians and military personnel in various parts of the world.<sup>1, 2</sup> The opportunity thus offered for intensive study has led to a better understanding of the nature of the disease and to certain radical changes in our point of view towards it.<sup>2, 3</sup> It has become apparent that infectious hepatitis may have more serious consequences than was thought in the past. Thus proper treatment assumes increased importance which is further enhanced by the demonstration that it can significantly influence the course of the disease and the prognosis. Although some of our observations have already been published<sup>2, 3</sup> the importance of this problem warrants a more detailed discussion than has previously been presented.

## MATERIAL AND METHODS

Our experience, gained largely in the army, is based on a systematic study of over 2000 cases of infectious hepatitis both in this country and in the Mediterranean Theater and the observation of some 6000 more. This material and the methods employed have been previously described.<sup>2, 3</sup> It is important to emphasize that this was a planned study and not simply a review of case records. For the evaluation of therapy, comparable groups of a single type, either acute hepatitis with jaundice, acute hepatitis without jaundice or chronic hepatitis of over three months' duration, were employed. Proper control studies were made of all laboratory and clinical procedures.

## THE SERIOUSNESS OF THE DISEASE

Since the seriousness of a disease is perhaps the most important factor in determining the need for careful or extended treatment, it is pertinent to examine the relevant evidence regarding infectious hepatitis.

*Mortality Rate.* Although the mortality rate during the acute stage has usually been low, varying between one to three cases per thousand, mismanagement and various complicating factors can markedly increase the risk. Thus Snell<sup>4</sup> has reported an 18 per cent mortality in a series of 32 consecutive cases.

*Duration of the Disease.* The duration of disability and of evidence of liver disease is prolonged. In our experience the period from onset of

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symptoms to reasonably complete symptomatic and clinical recovery averages about two months. Although under the best conditions the majority of patients should be well in six weeks, about 10 per cent will still be sick after three months. Laboratory evidence regarding the duration of liver disease is shown in table 1. During the third month after onset of symptoms 71

TABLE I

Findings in 180 Consecutive Cases of Acute Infectious Hepatitis during the Third Month Following Onset

<i>Bromsulfalein</i> (5 mg./kg.)	
Total cases tested	122
Normal	29%
3-4% dye retention in 1 hr.	20%
5-9% dye retention in 1 hr.	36%
10% plus dye retention in 1 hr.	14%
<i>Cephalin cholesterol flocculation test</i>	
Total cases tested	142
Normal	64%
1+ or 2+ in 24 hrs.	20%
3+ or 4+ in 24 hrs.	15%

per cent showed an abnormal bromsulfalein dye retention and in many of these this test was strongly positive. On the basis of present knowledge about one half of these patients failed to receive the best treatment but it was probably quite as good as that which the average case received before the war. Finally, the duration is substantiated by the persistence of histological evidence of inflammation.<sup>5, 6</sup>

*Residuals.* Residuals and sequelae are not uncommon and are of several sorts. The condition that we have described under the term "chronic active hepatitis"<sup>3</sup> which is characterized by intermittent periods of disability for months or years develops in from 5 to 10 per cent of properly managed acute cases. Under other circumstances we have seen the incidence as high as 28 per cent. The ultimate prognosis is unknown.

Undoubtedly a small number of cases develop some type of fibrosis or cirrhosis of the liver but this group is thought to be relatively small.<sup>6, 7</sup> On the other hand, late follow-up studies in "catarrhal jaundice" indicate that a substantial percentage of such cases suffer a permanent lowering of the liver reserve.<sup>8, 9, 10</sup> It is not unlikely, as suggested by Bloomfield,<sup>11</sup> that the milder acute cases, being the ones that receive little or no treatment, are the most likely to develop significant liver damage.

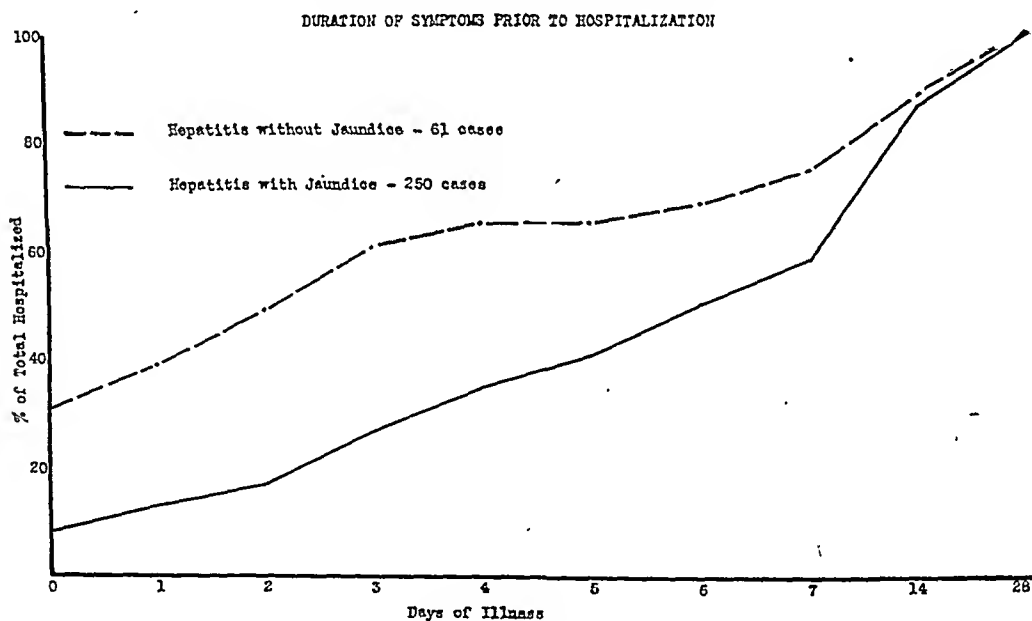
From the above data it must be concluded that infectious hepatitis is a disease of serious potentialities and should be treated accordingly.

### THE CARDINAL PRINCIPLES OF TREATMENT

In most cases of acute liver cell injury the diagnosis is made and treatment is begun only after a large proportion of the damage has occurred. Therapeutic efforts must therefore be directed towards the prevention of further damage and towards the aiding of natural reparative processes. Dramatically effective measures are not to be expected. Our experience

indicates that there are only three major therapeutic principles of proved value in infectious hepatitis. These are bed rest, diet and the avoidance of additional factors injurious to the liver.

*Bed Rest.* Detailed evidence regarding rest and exercise in hepatitis will be presented elsewhere.<sup>12</sup> Suffice it to say that we were the first to demonstrate that in the presence of active hepatitis, exercise will produce an exacerbation of the disease.<sup>2</sup> Thus, failure to go to bed during the acute icteric stage has apparently caused cases of only moderate severity to progress to a fatal outcome over a period of weeks. In other instances the severity and duration have apparently been greatly increased. In the convalescent stage, after jaundice has cleared and the physical findings and symptoms have become minimal, but before sufficient recovery has occurred, exercise may induce a return of jaundice with a severe and prolonged clinical relapse.<sup>2, 12</sup> Finally, cases of acute hepatitis put to bed during the first few days of illness apparently are less likely to develop jaundice than those who remain ambulatory. This is shown in graph 1 where the rate of hospitalization in

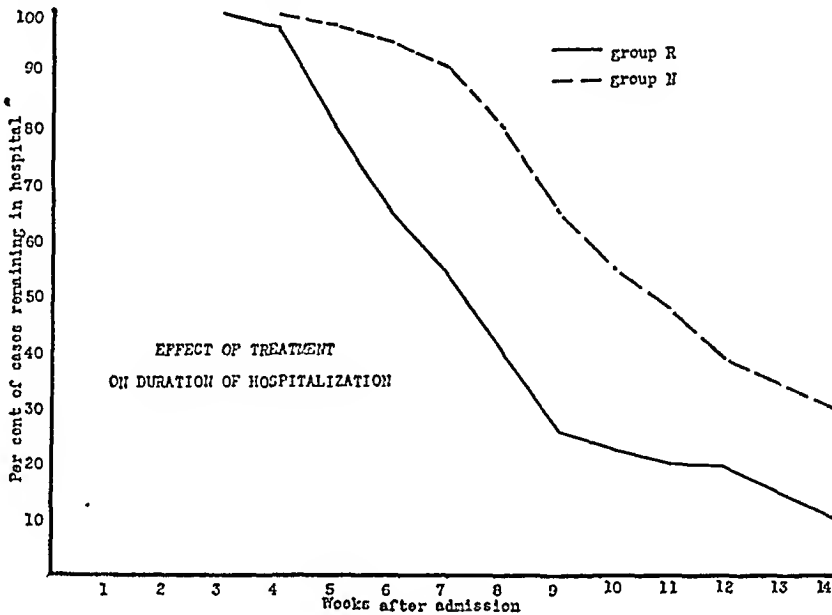


GRAPH 1.

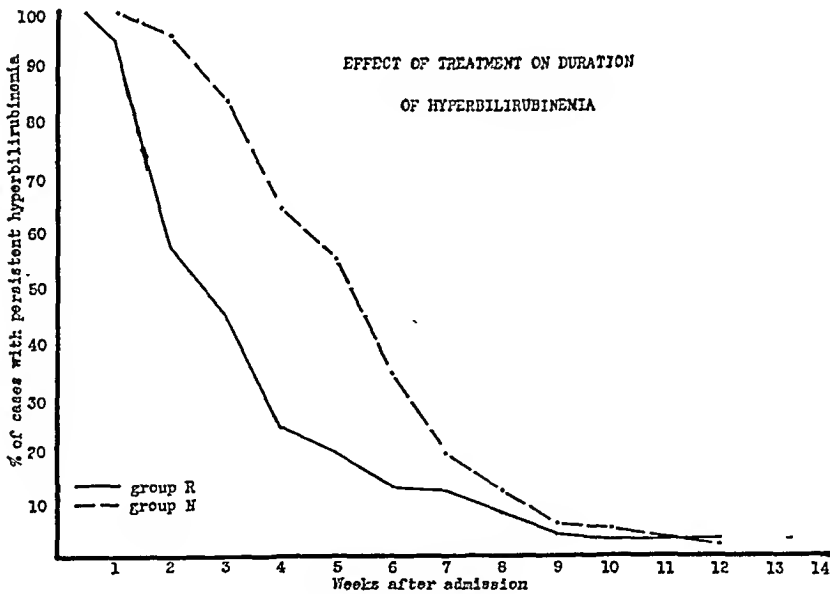
relation to the duration of symptoms has been plotted separately for acute hepatitis with jaundice and acute hepatitis without jaundice. Three hundred eleven consecutive acute cases were included. Since in this instance, jaundice is a sign of comparative severity, it is clear that exercise has a deleterious influence very early in the disease. In fact, there is evidence from infected volunteers<sup>13</sup> that those who exercise shortly after exposure are more likely to develop the disease.

As would be expected from the above data it has repeatedly been observed that patients who remain at strict bed rest for an adequate period of time

recover more promptly and more regularly, while those who have only a short period of bed rest or fail to keep strictly in bed have a longer period of illness and are much more likely to develop the chronic form of the disease. This is demonstrated in graphs 2 and 3. Here are shown the duration of



GRAPH 2.



GRAPH 3.

hospitalization and the duration of hyperbilirubinemia in two carefully studied and comparable series of cases of acute hepatitis with jaundice. Group "N" consisting of 81 cases had poor bed rest whereas group "R" including 74 cases had strict and adequate rest. In addition group "N" re-

ceived the usual average protein, low fat and high carbohydrate diet but group "R" ate a high protein, moderate fat and high carbohydrate diet. It is impossible, of course, to determine the relative rôles of diet and rest in these groups. Although both were probably factors it is felt that rest was the more important. Hughes has made similar observations on smaller groups with essentially the same results.<sup>14</sup> It will be noted that not only was recovery more rapid in group "R" but that the percentage remaining in the hospital at the end of the period of observation, 14 weeks, was much smaller. This last figure includes the so-called chronic cases.

For practical purposes bed rest should be instituted as early in the disease as possible and should be maintained until the criteria to be discussed later are met. It should be as strict as feasible. Bathroom privileges are permissible in all but the seriously ill.

*Diet.* There is ample experimental evidence that a diet high in protein is most desirable in acute liver injury.<sup>15, 16, 17</sup> We believe, as does Hoagland,<sup>18</sup> that for the present there is insufficient evidence concerning the harmful effects of fat to warrant more than moderate restriction. However, an excess of fat other than butter fat in the diet is poorly tolerated and may result in severe anorexia. Carbohydrates should be high in order to spare protein as well as to provide calories.

It has not been possible to demonstrate the effect of diet as clearly as in the case of rest. The improved results obtained in group "R" over group "N" (graphs 2 and 3) are in all probability due in part to the change in diet. However, the high protein diet was more appetizing so that the total caloric intake was greater. Thus we cannot be certain that the proteins played a dominant rôle although this seems likely on theoretical grounds. In another less carefully controlled investigation involving two groups of cases of about 25 patients each where the only variable factor was the diet there was a significant difference in the duration of the disease in favor of those on the high protein diet. Finally, it was repeatedly observed that patients who were under-nourished at time of onset of the disease were likely to be severe cases and that underweight patients who failed to gain weight usually ran a protracted course. It thus appears that malnutrition which probably involved a deficiency in protein was an important factor influencing the degree and duration of liver injury in many of our cases.

In civilian practice where most patients are well nourished, diet is probably a less important factor. However, it may become of great importance where malnutrition is present or where there is prolonged anorexia and failure to eat. In the latter case it is desirable to provide protein in the form of plasma or amino acids by vein. For the average case a diet of protein 200 grams, fat 65 grams, and carbohydrate 300 grams is recommended. This amount of protein is readily obtained by the liberal use of skimmed milk powder and cottage cheese. Enough fat in the form of butter and cream must be employed to make the diet palatable.

The addition of methionine or choline has not produced clear cut results

either in our experience or in that of others.<sup>13</sup> This is probably because in man there is rarely a sufficient degree of deficiency in these substances to allow for a demonstrable effect in the small sized groups in which it has been employed. In certain chronic forms of liver disease the situation, however, may be different.

*Avoidance of Additional Liver Trauma.* The third principle of treatment is the avoidance of additional liver trauma. An already injured liver is extremely sensitive to toxic agents which ordinarily would have little effect. This is especially important during the prodromal and early icteric stages when the maximal degree of acute liver cell damage is present. At this point in the disease additional liver trauma may result in acute liver failure and death. Later in the course, an exacerbation is the usual result.

The most common causes of additional trauma are surgical operations, secondary infections and exposure to various toxic substances, notably alcohol. The first is probably injurious to the liver both because of factors connected with the tissue trauma incident to surgery and because of the anesthetic. Ether, chloroform and possibly ethylene are probably the most dangerous anesthetics. In case of emergency, local or spinal is recommended.

Secondary infections of all varieties have a deleterious effect in infectious hepatitis. This is especially true of malaria, diarrheas and virus pneumonia which by themselves produce marked alterations in liver function indicating liver injury even in the normal liver. As far as possible they must be avoided or promptly controlled. In this connection we have found that the incidence of respiratory infections is about twice as high in hepatitis wards as in other medical wards, indicating a lowering of resistance.

Alcohol is contraindicated in all stages of hepatitis. It has frequently been observed to produce severe exacerbations. Saline purges and other cathartics appear to be harmful, probably because of the associated diarrhea. Enemata should be employed for constipation. Opiates and the short acting barbiturates that are probably detoxified or excreted by the liver have a prolonged and exaggerated effect in the presence of liver disease. We have seen acute fatal morphinism after  $\frac{1}{2}$  grain and have seen patients sleep for 36 hours after 3 grains of amytal. Whether these and similar drugs damage the liver is uncertain but they must be used with caution.

To summarize, early and prolonged bed rest, adequate protein intake, and avoidance of additional liver injury throughout the course of the disease are the cardinal principles of treatment. In the interest of clarity the details of management in each stage will be discussed separately.

#### PRODROMAL STAGE

The chief problem in this stage of the disease is the question of diagnosis.<sup>18</sup> When there is reasonable suspicion of infectious hepatitis it is best to treat the case as such and await developments. Confirmatory findings, especially jaundice, should appear within 10 to 14 days. If at the end of this time the

diagnosis cannot be established the patient should be allowed out of bed and carefully watched for at least a week. The development of a large and tender liver or other evidence of liver pathology as manifested by aggravation of liver function tests indicates the presence of hepatitis and the patient must be immediately returned to bed.

Treatment in this period is symptomatic except for rest and diet. Particular care must be used to avoid additional liver injury. This point requires emphasis because patients in this stage of the disease are potentially much more seriously ill than they appear. Relatively minor operations especially under ether may precipitate liver failure and death. Occasionally these are performed for some unrelated condition on the assumption that the patient has recovered from a mild acute respiratory or gastrointestinal infection. In other instances hepatitis may produce a picture simulating acute appendicitis, cholecystitis or ruptured peptic ulcer. It is well to remember that acute abdominal pain and rigidity occur only, in our experience, in the presence of an enlarged and tender liver.

#### ACUTE ICTERIC STAGE

The appearance of jaundice usually settles the diagnosis. Since it is impossible to predict the degree of severity for a few days to a week or more after the appearance of icterus or until the bilirubinemia has reached its peak and has commenced to fall, it is best to treat all cases as potentially severe until proved otherwise. Strict bed rest must be enforced. A high protein intake should be maintained, if necessary by the use of intravenous amino acids or plasma. This is especially desirable where nausea and vomiting last for more than a few days. Glucose can be given in a similar fashion.

In our experience the acute symptoms associated with the appearance of jaundice are best controlled by maintaining a fluid intake of at least 3000 c.c. daily. Chilled skimmed milk is especially desirable because it supplies both protein and fluid and is well tolerated. If fluids are given intravenously it is important to avoid normal saline since marked aggravation of the size and tenderness of the liver and even generalized edema is readily produced. As is well known there is a definite tendency towards fluid retention in this disease and we have often noted increase in the liver size when fluids are pushed by mouth. Thus, it is best to employ 5 or 10 per cent glucose in water for intravenous use except where vomiting is severe when salt may be used with caution. Forcing of fluids usually results in prompt abatement of symptoms within a few days.

Although the immediate prognosis is difficult to determine at the beginning of jaundice, a history of previous liver injury, age over 40 years, poor nutritional condition and the presence of complicating infections are suggestive findings. A bilirubinemia that rises rapidly for four or five days to high levels especially in the absence of a prodromal period and a persistently high bilirubinemia for a week or more associated with persistent nausea and vomiting are also suggestive signs. We have been able to show



a definite correlation in several large series of cases between the maximum icterus index and the severity and duration of the disease. Thus when the icterus index rises to 100 or more, recovery will require over three months in 50 per cent of cases.

In the more serious cases vitamin K should be given if the prothrombin time is elevated or if bleeding is noted. The dose should not be over 5 mg. parenterally as Shapiro<sup>19</sup> has shown that larger amounts may depress liver function. If the prothrombin time continues high, transfusions are indicated. Hypoglycemia must be watched for and treated by the frequent or constant administration of glucose. Occasionally ascites is seen in severe acute cases. This rarely requires special treatment except for care in the administration of salt and fluids. It does not indicate that cirrhosis is present since it spontaneously disappears as recovery progresses.

Certain additional points regarding therapy should be mentioned. Cathartics and especially salts are contraindicated. Bile salts are without benefit and may be harmful. Atropine is to be preferred to opiates for cramps which are sometimes troublesome. In severely ill cases salicylates may further increase the prothrombin time to dangerous levels.<sup>20</sup> There is evidence that thiamine chloride in large doses may be toxic to the liver,<sup>15</sup> so it is best to use only small doses parenterally if at all. Since it has been found that the sulfa drugs may be toxic to the liver at least in certain individuals,<sup>21, 22</sup> penicillin is to be preferred for complicating infections requiring specific therapy.

### ACUTE HEPATITIS WITHOUT JAUNDICE

This mild form of acute infectious hepatitis runs a shorter course than the more severe icteric type. However, the principles governing management are identical. If treatment is not strictly enforced, which is often difficult, the course is unnecessarily prolonged and sequelae may occur.

### CONVALESCENT STAGE

The importance of maintaining the hepatitis patient on bed rest until recovery is sufficiently advanced has already been discussed. The practical question is how to determine when this point has been reached. Obviously, if a patient with certain abnormal findings while at bed rest is allowed to return to work after an appropriate interval on an ambulatory status and then develops an exacerbation or relapse of his hepatitis, his original findings can be said to have indicated persistent activity of his liver disease. In order to insure controlled conditions a graduated exercise tolerance test was substituted for the return to work and a careful study made of the relation of initial findings to the outcome of the test.<sup>2, 12</sup> The first series of patients, consisting of 184 consecutive cases of infectious hepatitis, were tested when they had reached a stage of recovery considered satisfactory by the local ward physician on the basis of pre-war criteria.

TABLE II

Significance of Various Findings Prior to Exercise in Relation to Outcome of Exercise Tolerance Test

Finding	Number of Cases	% Pos. Exer. Tol.
1. Liver normal size	106	31
Liver borderline size	38	45
Liver enlarged (non tender)	40	75
2. Normal bromsulfalein (5 mg./kg.)	32	34
3-4% retention in 1 hr.	21	43
5-9% retention in 1 hr.	31	48
10% plus retention in 1 hr.	11	91
3. Negative Hanger test	115	38
1+ or 2+ positive (24 hrs.)	12	50
3+ or 4+ positive (24 hrs.)	24	62
4. Normal alkaline phosphatase	69	48
4.0 or more Bodansky units	20	75
5. Normal sedimentation rate	86	45
Elevated sedimentation rate	30	53

An analysis of these results is presented in table 2. Forty-three per cent of the 184 cases had an abnormal test, equivalent to an exacerbation of the hepatitis, demonstrating the inadequacy of our original criteria for recovery. It will be noted that marked elevation of the bromsulfalein and enlargement of the liver are the most significant findings whereas elevation of the sedimentation rate is of little value. Also, active hepatitis may be present even though the liver and the bromsulfalein retention are normal prior to exercise. This is only partly explained by many patients having more than one positive finding. The value of further intercorrelations is limited by the numbers involved but it appears that liver enlargement or abnormal bromsulfalein retention alone is frequently significant whereas an abnormal phosphatase level or cephalin cholesterol flocculation alone is usually not.

Serum bilirubinemia is not included in the above table because of the inaccuracy of icterus index determinations at low levels. Unfortunately it was impossible to use an accurate method routinely in this particular group. Patients with clinical jaundice were never deliberately exercised. Subsequent observations, however, show that an icterus index over 20 units or a prompt direct Van den Bergh reaction is practically always associated with active hepatitis. On the other hand an elevated indirect type of Van den Bergh can only be classified as suggestive of activity. In addition to the above findings the persistence of symptoms, the presence of complicating infections, a history of previous liver damage or if the preceding acute attack was severe or in a person over 40 years of age increase the probability of persistent activity of the hepatitis.

As a result of this study the following criteria were formulated to be met before the termination of bed rest. They are applicable equally to acute hepatitis with and without jaundice.

*Criteria for Ambulatory Status.* (1) At least three weeks' bed rest. (2) Liver—not enlarged and not tender. (3) Absence of symptoms especially lassitude, diarrhea, intestinal cramps, flatus, headache and anorexia.

(4) Normal serum bilirubin for one week. If slightly elevated, the direct Van den Bergh must be negative. (5) Bromsulfalein under 10 per cent in one hour (5 mg./kg.—dose) and preferably under 5 per cent.

Also, if available, the cephalin cholesterol flocculation test should be 2+ or less in 24 hours and the alkaline serum phosphatase under 4.0 Bodansky units. If only one finding is positive keep patient in bed one extra week and then try on ambulatory status.

Even when the above criteria are met, some 10 per cent of patients will still show an abnormal exercise tolerance test. Consequently, it is felt that these criteria are not too drastic for civilian practice. It can be argued that since civilian patients may be returning to sedentary jobs their recovery need not be as complete as in the army. To some extent this is true and we are well aware that there are patients who can return to work after only a week in bed, but it is impossible to select these cases beforehand. Recent experience with civilians has confirmed our observations in the army.

In civilian practice an exercise tolerance test is not necessary or feasible as an index of recovery, but, as a substitute, patients should be followed carefully for several weeks after returning to work to insure proper convalescence and determine if they have really recovered. If a significant degree of active hepatitis is still present as indicated by the development of an enlarged tender liver or a sharp increase in the bromsulfalein retention the case should be returned to bed at once. If this is not done disability will persist for several months at least and not infrequently we believe that chronic hepatitis will develop.

### CHRONIC HEPATITIS

The management of this stage of infectious hepatitis has been previously discussed in some detail.<sup>3</sup> Due to the very slow rate of recovery it is necessary to be more conservative in the interpretation of the "criteria of recovery" than in the acute disease. Table 3 shows that other findings being equal a case of chronic hepatitis is almost twice as likely to have an abnormal exercise tolerance as an acute case.

TABLE III

Relation of Type of Hepatitis to Outcome of Exercise Tolerance Test

Finding	Number of Cases	% Pos. Exer. Tol.
1. Acute hepatitis	130	36
Chronic (3 mo. plus) hepatitis	54	61
2. Liver normal or borderline in size in acute hepatitis	103	28
Liver normal or borderline in size in chronic hepatitis	41	51

It is important to eliminate all complicating infections. Dental and other foci, amebiasis and malaria should always be ruled out. Non-specific diarrhea, if present must be controlled even if it appears to be the result of the hepatitis. Often this can be accomplished with vioform, sulfaguanidine or dilute hydrochloric acid by mouth. Sometimes crude liver extract intra-

muscularly is effective suggesting that the diarrhea is related to some form of nontropical sprue.

Good nutrition must be maintained. Patients that are underweight and fail to gain rarely do well. The regular hepatitis diet should be used but with particular emphasis on the total caloric intake. Hoagland<sup>18</sup> has suggested intravenous liver extract. In our experience this treatment is difficult to evaluate but it apparently is of benefit in some cases. The same can be said of choline and methionine.

Patients with so-called inactive hepatitis,<sup>3</sup> that is with evidence of liver damage but with a normal reaction to exercise, do not require bed rest. It is, however, desirable for them to follow the dietary treatment.

### DISCUSSION

It is of interest to speculate as to why infectious hepatitis appears to be more severe at present than formerly. If is, of course, quite possible that we are now dealing with a different virus or perhaps a more virulent strain. The age factor is of some importance since our cases have been entirely adults where the disease is probably more severe than in children. On the other hand, obvious signs even of severe liver disease are few and the clinical picture of chronic hepatitis has until recently been obscure.<sup>3</sup> Perhaps sequelae occurred but were unrecognized or misdiagnosed. In this connection it should be mentioned that extensive experience during the last year in this country both in the army and among civilians has revealed no essential differences in the disease from that which we studied in Africa, Italy, France and the Near East during the war.

Perhaps the most important result of the study lies in the application of findings made in infectious hepatitis to other etiologic types of acute liver disease. Infectious mononucleosis, virus pneumonia, acute brucellosis and probably many other infections are frequently associated with liver injury. It is not unlikely that residual symptoms are often due to a residual hepatitis, much of which might be averted by paying more attention to the liver and by applying the principles of management that we have learned from infectious hepatitis.

### SUMMARY

1. Evidence is presented to show that infectious hepatitis is a more serious disease than was previously thought and that it therefore should be treated accordingly.

2. The cardinal principles of treatment are early, strict and sufficient bed rest, high protein, moderate fat and high carbohydrate diet and avoidance of additional liver trauma. Evidence is presented to show that these measures are effective in reducing the duration of the disease and the incidence of relapse and chronicity.

3. Details of management in the different stages of the disease are discussed.

4. The problem of determining when recovery has become sufficiently advanced to allow the patient out of bed has been investigated by means of an exercise tolerance test. This has resulted in the formulation of a set of criteria which differ materially from pre-war ideas. Their use results in 90 to 95 per cent of cases making a prompt and satisfactory clinical recovery.

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# REFLEX SYMPATHETIC DYSTROPHY; REPORT ON 57 CASES \*

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REFLEX sympathetic dystrophy is usually referred to as causalgia because of its chief symptom—an agonizing burning pain. The former term is preferable, however, because in many patients with reflex sympathetic dystrophy the distinguishing features are not pain but other manifestations of sympathetic stimulation, namely, rubor, pallor, or both, swelling, sweating and often mottled or cystic atrophy of the bone. Atrophic changes in the skin and muscles may be prominent. The characteristic feature of sympathetic pain is its deep, burning nature, felt diffusely through the part affected, often occurring in acute exacerbations on use of the limb or on pressure over trigger points. A less frequent painful feature may be muscle cramp. A background of vasomotor instability is very common, together with a hyperemotional temperament or even hysterical stigmata that frequently lead to a mistaken diagnosis of psychoneurosis. This fact has often led to many injustices to the patient, both personally and in the settlement of industrial cases.

A case in point concerns a patient who sprained her arm lifting heavy drums over her head. Thrombophlebitis of the brachial and subclavian veins followed. For a year she suffered severe pain in the upper arm, became highly hysterical and emotional and was turned down before the industrial commission for proper compensation. When she was first examined, rubor of the lower arm and hand was present, together with swelling and increased sweating. Two cervical sympathetic metycaine blocks gave her 90 per cent relief of pain, together with disappearance of definite trigger points. For some reason unknown to me I never could persuade her lawyer to reopen her case.

Mitchell, Morehouse and Keen wrote the first brilliant description of this distressing phenomenon, based on cases of gunshot wounds to nerves and blood vessels in the Civil War. Sudeck described cases of painful joint involvement, giving rise to the term Sudeck's syndrome. Leriche pointed out most vividly the rôle of the sympathetic system in this pernicious reflex, and Homans, in his presidential address to the Massachusetts Medical Society in 1940, described the clinical features and the successful treatment of several cases of "minor causalgia." To Livingston, in his scholarly monograph on "Pain Mechanisms" credit should be given for the clearest theoretical elucidation of the reflex itself. I have borrowed heavily from his theory to explain the vicious circle producing the syndrome of reflex sympathetic dystrophy in the diagrams and ideas expressed in this article.

\* Read at the Twenty-seventh Annual Session of the American College of Physicians, Philadelphia, May 15, 1946.

De Takats has recently reviewed 54 cases of causalgic states, in which he recognizes three sensory levels, peripheral, spinal and cortical, based on lesions of the first, second and third neurons. He advocates direct treatment to the affected neuron. With few exceptions our therapeutic attack has been on the second neuron, namely the sympathetic pathway, either by sympathetic metycaine block or by sympathectomy. It is our conviction that the majority of these patients can be relieved by these two therapeutic methods. In severe causalgic states treatment of the trigger points alone is not very satisfactory in our experience, and has been used chiefly as an adjunct to metycaine block and sympathectomy.

### MECHANISM OF REFLEX SYMPATHETIC DYSTROPHY

Figure 1 illustrates diagrammatically the nervous pathways giving rise to the syndrome of reflex sympathetic dystrophy. The fundamental concept of the internuncial pool (figure 2), a theory advanced by Lorente de No and adopted by Livingston, can be explained simply as follows. A prolonged bombardment of pain impulses sets up a vicious circle of reflexes spreading through a pool of many neuron connections upward, downward and even across the spinal cord, and perhaps reaching as high as the thalamus itself. In accordance with the principle of "summation of nervous impulses," and with the theory of "facilitation" of conductivity within the spinal cord as described by Porter and Taylor, there is kept alive within such a pool a constant circling of activity across the synapses involved. Some of these synapses include the sympathetic motor neuron cells in the lateral horn, controlling vasomotor tone and the sweat glands. Spasm in the arteriolar and the venule ends of the capillary loops raises filtration pressure, and edema and swelling result. Cyanosis and anoxemia increase capillary permeability and filtration, further augmenting edema. Other synapses involved may be the anterior motor horn cells, giving rise to skeletal muscle cramps and spasms. Augmented stimuli to pain also flow out of the pool, traveling up the thalamic tract. Depending on the extent of the pool, we detect the phenomena of pain and sympathetic disturbances observed a long distance from the injured area of the body and occasionally even spread to the contralateral side.

### ETIOLOGY

The source (table 1) of the reflex sympathetic dystrophy syndrome was traumatic in 31 of our 57 cases; secondary to operative procedures in six; to static defects of the foot in four; to thrombophlebitis in five; and to a scalenus syndrome accompanied by a Raynaud's syndrome in two. The traumatic cases were divided as follows: fractures 12; sprains 12; bruises 5; lacerations, occupational trauma and bismuth injection outside of vein in one each. Under operative procedures, there were four amputations; one mangled hand and amputation of a finger; and one ligation of a varicose

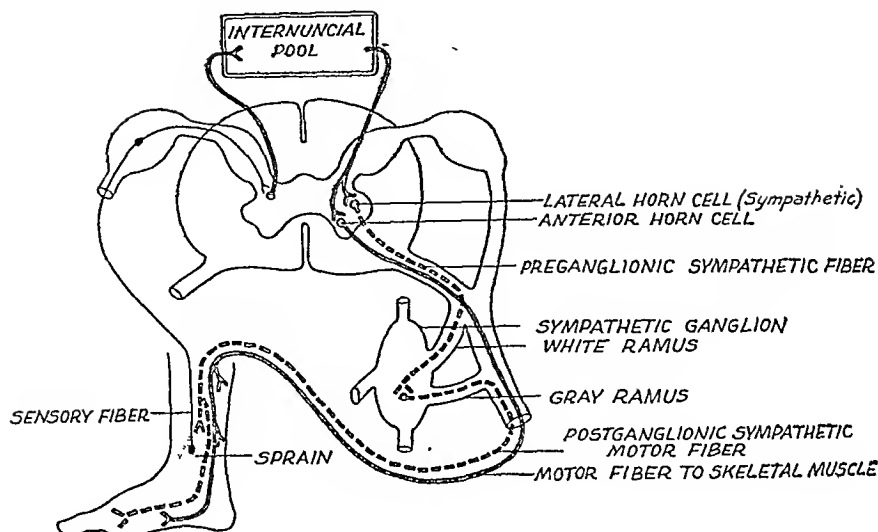


FIG. 1. Diagram of nervous pathway of reflex sympathetic dystrophy. The afferent pathway is represented on the reader's left, the efferent on the right. Below the anterior horn, the open line represents the sympathetic fibers, the heavy solid line the motor nerves. (From Surg., Gynec. and Obst., Jan., 1946.)

### INTERNUNCIAL POOL Closed Self-reëxciting Chain

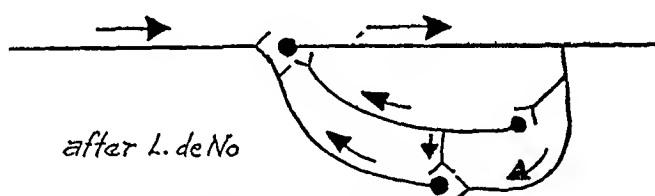


FIG. 2. Diagram of de No's theory of the internuncial pool. (Adapted from Jr. Neurophysiol., 1938, i, 207.)

TABLE I  
Etiology in 57 Cases

Traumatic .....	31
Fracture .....	12
Sprain .....	12
Bruise .....	5
Laceration .....	1
Occupational .....	1
Bismuth injection outside vein .....	1
Operative procedures .....	6
Amputation .....	4
Mangled hand and amputation .....	1
Ligation varicose vein, ulcer at site .....	1
Static defect of foot .....	4
Thrombophlebitis .....	5
Spontaneous hematoma involving peroneal nerve .....	1
Malum coxae senilis, nailing of hip .....	1
Osteomyelitis .....	1
Thalamic syndrome, cerebral hemorrhage .....	1
Plantar wart .....	1
Gonorrheal arthritis .....	1
Scalenus syndrome with Raynaud's syndrome .....	2
Anterior poliomyelitis .....	1
Subacromial bursitis .....	1
Intervertebral disk herniation .....	1



vein, resulting in a chronic ulcer at the site of operation. There were single cases with the following diagnoses: spontaneous hematoma, involving the peroneal nerve in a patient with hypoprothrombinemia resulting from non-tropical sprue; malum coxae senilis and nailing of the hip; osteomyelitis; thalamic syndrome due to cerebral hemorrhage; plantar wart; gonorrheal arthritis; anterior poliomyelitis of 25 years' duration; subacromial bursitis complicated by angina of effort; intervertebral disk herniation.

Exacerbating factors were operative procedures in seven cases, fungus infection in three, pes planus in two, thrombophlebitis in two and, in one case each, osteomyelitis, scalenus syndrome and angina of effort.

## PAIN

Pain is almost always present and may be so severe and so long persistent that the patient contemplates suicide. Causalgic pain mediated by the sympathetic system has characteristic features of its own. It is a deep, boring "toothache-like" pain, diffuse in its distribution, difficult for the patient to localize, not felt precisely in the area of the old injury. Manipulation, as in physiotherapy, and use of the limb involved, aggravate the suffering. As stated previously, the pain is often described as "burning." One or more trigger areas are present. These trigger zones may be widely separated and some of them far from the site of original injury. A chief trigger zone is usually found near the original injury, however, and blocking this area with procaine may cause the other trigger points to disappear. Thus, blocking a trigger point is an additional diagnostic and therapeutic method of attack. Pressure on a trigger point characteristically causes a diffuse spread of the pain over a wide area, usually cephalad.

TABLE II

### Pain

Severe or causalgic .....	34
Moderate .....	21
None .....	2
Trigger points .....	36

In our 57 cases (table 2), trigger points, single or multiple were found in thirty-six. Pain was severe or causalgic in 34, moderate in 21 and absent in two. These last two patients showed other signs of reflex sympathetic dystrophy.

## OTHER SYMPTOMS AND SIGNS (TABLE 3)

Rubor was a more frequent finding than pallor in our patients, although they more often complained of a cold than of a hot limb. Rubor was present in 30, pallor recorded in 13, and swelling in thirty. Increased sweating is a very important indication of sympathetic stimulation and should always be carefully sought for, both by questioning and by observa-

TABLE III

## Other Symptoms and Signs

Rubor .....	30
Pallor .....	13
Swelling .....	30
Sweat .....	29
Atrophy	
Skin .....	8
Muscle .....	14
Bone	
Mottled or cystic .....	9
Diffuse (disuse) .....	9
Cramp .....	4

tion. This feature was present in 29 of our patients. Atrophy of the skin was seen in eight and atrophy of the muscle in 14 cases. The typical bone atrophy of reflex sympathetic dystrophy has a mottled or cystic appearance in roentgen films (figure 3). The atrophic changes are probably due to spasm of the nutrient arteries. The findings are typical of the so-called Sudeck's arthritis. Such changes were noted in the roentgenograms of nine patients. A diffuse atrophy of disuse was seen in another nine cases. Four patients had muscle cramps, this feature being more often seen in those who have had old deep thrombophlebitis.

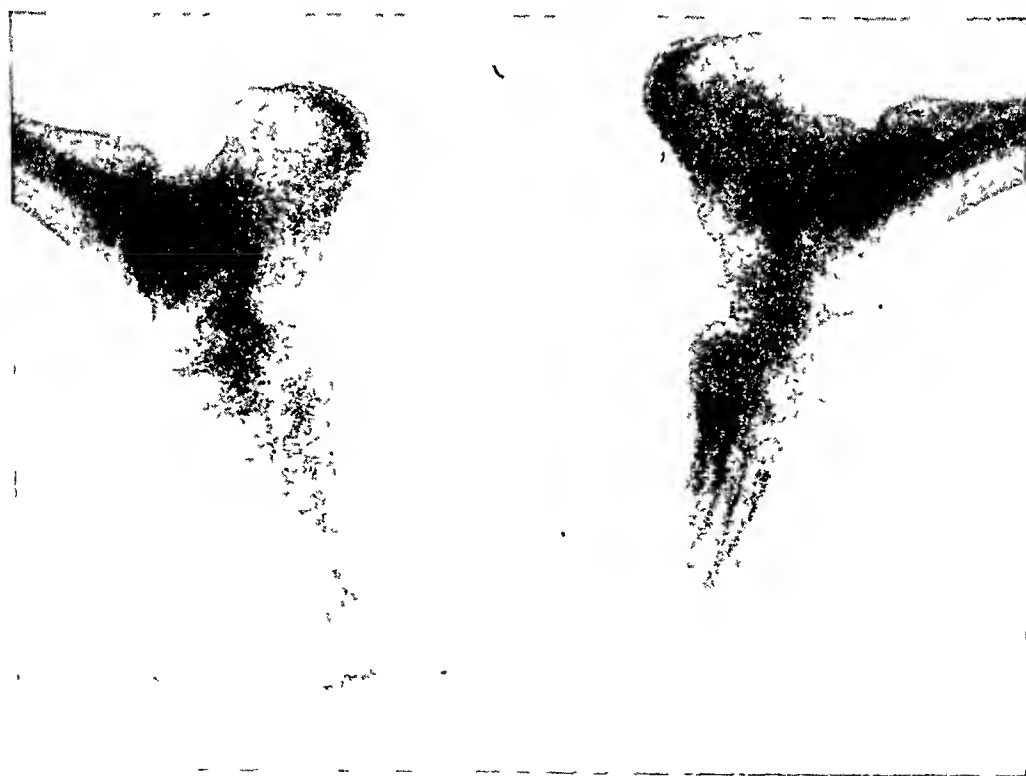


FIG. 3. Mottled bone atrophy of Sudeck's arthritis. Sprain of left foot five months before. Improvement spontaneously three months after this roentgenogram was taken. Right foot shown for contrast.

## DIAGNOSIS

Either cervical or paralumbar sympathetic procaine block will serve as a diagnostic therapeutic test. The relief of pain may be almost miraculous but even if not so dramatic will serve to establish the diagnosis, provided disappearance of other phenomena is also noted, such as relief of sweating, increased warmth and comfort in a cold member associated with rise of skin temperature (temperature index test); and disappearance of trigger points (figure 4).

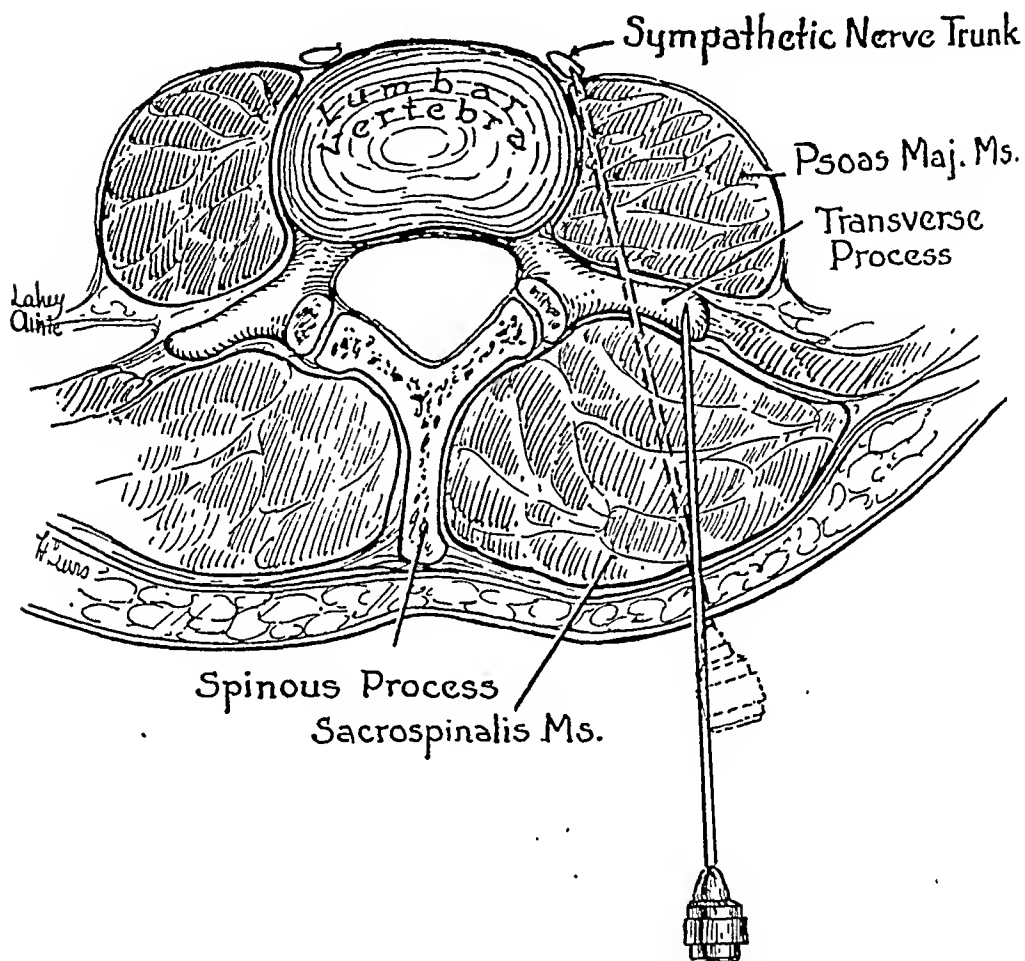


FIG. 4. Technic of paralumbar metycaïne sympathetic block. (From Nicholson, *Anesth. and Analg.*, May-June, 1942.)

## TREATMENT

The ideal point of attack would be the internuncial pool itself. So far, no direct effective means is at hand to stop the vicious circle within this pool of neuron synapses.

Two other points of attack exist: the trigger points and the sympathetic pathway. Repeated injections of the trigger points usually are necessary.

If the sympathetic pathway is blocked by procaine, one is occasionally gratified by the astounding relief obtained with only one injection. More often, there are relapses within a few days or weeks and repeated injections are necessary at longer and longer intervals. It would seem more logical to give a series of three injections, one every second day, for the permanent rupture of the pernicious reflex, a method so successfully applied to thrombophlebitis.

At the Lahey Clinic we have felt it best to resort to sympathectomy in the majority of our treated cases, after the demonstration of the efficacy of one block, in order to obtain the maximum of relief and the greatest assurance of permanency of relief.

Posterior root rhizotomy, cordotomy or, for pain from a high cervical segment, interruption of the thalamic pathways in the medulla and even resection of the sensory cortex may be necessary in exceptional cases. In none of our cases have we resorted as yet to these more radical measures, although in one unsuccessful result after sympathectomy, we are considering interruption of the thalamic tract. This was the case of a woman who had suffered a laceration of the hand, and two repair operations one year before. She had severe causalgic pain. Trigger points, pallor, sweating, muscle and bone atrophy were present. Sympathetic block gave no relief and a year after sympathectomy there was no relief. She is to have resection of the operative scar on the wrist with a pedicle skin graft done before interruption of the thalamic tract will be carried out.

TABLE IV

Results of Block on Pain in 36 Patients

Block as only therapy .....	12
100% Relief for 1 month or more .....	4
100% Relief—follow-up less than 1 month .....	5
90% Relief for 1 month or more .....	1
50-90% Relief—follow-up less than 1 month .....	1
Temporary relief—sympathectomy refused .....	1
Block with temporary relief and sympathectomy done later .....	24

Twenty-four patients (table 4) received sympathetic procaine block, with varying amounts of relief of pain and sympathetic phenomena in all but two. Twelve patients were treated by block alone. Of these, four obtained complete relief for one month or over and five who were followed less than one month received at least temporary complete relief. One patient had 50 to 90 per cent relief for one month or over, and another patient the same amount of relief, though she has had a follow-up of less than one month. One patient received temporary relief after metycaine block as the only method of therapy and refused sympathectomy. Another patient who had injection of trigger points as well as sympathetic procaine block obtained relief for only three weeks and sympathectomy was performed later.

TABLE V

## Results of Sympathectomy on Pain in 29 Patients

100% Relief 1 month to 2 years .....	10
100% Relief—follow-up less than 1 month .....	1
50-90% Relief 1 month to 2¼ years .....	11
0-25% Relief more than 1 month .....	7

Twenty-nine patients have undergone sympathectomy (table 5). Ten obtained complete relief for follow-up period of from one month to two years. One patient received complete relief but was followed for less than one month. Eleven patients had 50 to 90 per cent relief for periods ranging from one month to two and a fourth years. Seven patients received little or no relief and were followed over one month.

An analysis of the seven poor results from sympathectomy is shown in table 6. Five obtained no relief whatsoever. In two of these, diagnostic

TABLE VI

## Analysis of Poor Results from Sympathectomy

No relief .....	5
Diagnostic block gave no relief (casts doubt on diagnosis) .....	2
Diagnostic block not done first .....	1
Scalenectomy needed .....	1
Angina of effort returned .....	1
25% relief only .....	2
Exploration of radial nerve advised .....	1
Continued physiotherapy for pronated feet, advised .....	1

blocks had given no relief either. One of these two patients has been discussed. The second patient who received no relief from either block or sympathectomy had sustained a fractured right ankle three years before. Her pain was severe, of the causalgic type; trigger points, rubor and swelling were present. For three months following sympathectomy she was considerably better and was able to abandon crutches. At a nine month follow-up examination, however, her pain was as severe as ever, although a good sympathectomy effect was evident and swelling was no longer present. This patient is to be tested by a peripheral peroneal and sural nerve block. The electrical resistance of the skin is to be studied for evidence of regeneration of the sympathetic nerves. She also needs operative correction of the foot, but our experience with such operations has been disappointing unless the causalgic state has first been cured.

Our experience with these two patients will make us hesitate in the future to offer sympathectomy to patients who received no relief following sympathetic block.

The third patient who had no relief following sympathectomy had his operation done elsewhere, without diagnostic block as advised by us, being carried out first. A fourth patient we feel needs a scalenectomy for further relief. The fifth patient who received absolutely no relief from sympathectomy suffered a peculiar pain in the left arm, axilla and chest, often

provoked by effort but more often coming on while lying down. Successful treatment of a left subacromial bursitis gave him no permanent relief. Three paravertebral sympathetic metycaine blocks and two trigger blocks gave him complete but temporary relief. An upper thoracic, left sympathectomy afforded him relief for only two or three weeks, and two months later he reported full return of angina of effort.

In two patients who received only about 25 per cent relief following sympathectomy, an additional exploration of the radial nerve is advised for one patient and the other needs continued physiotherapy for pronated feet.

Most unfortunately, a cervical sympathetic block in one patient resulted in an injury to the spinal cord, giving rise to a Brown-Sequard syndrome, leading to disability and pain in the left arm and right leg. He has, however, been free from his old causalgic pain for a year. Another patient has developed a Raynaud's syndrome one year after relief by block alone of causalgic pain resulting from thrombophlebitis. Spontaneous improvement without therapy was noted in two patients.

### SUMMARY

Reflex sympathetic dystrophy is described as a syndrome produced often by minor trauma to a limb or local disease, leading to the reflex production of the sympathetic phenomena of rubor or pallor, heat or cold, increased sweating, edema, and pain. Since the factor of pain may be absent, the term reflex sympathetic dystrophy is preferred to causalgia.

The rôle of Lorente de No's "internuncial pool" in the production of the syndrome of reflex sympathetic dystrophy is presented.

Traumatic injury accounted for only 54.4 per cent of the 57 cases reported.

The typical bone atrophy of reflex sympathetic dystrophy is mottled or cystic (Sudeck's syndrome).

Diagnosis depends largely on the demonstration of relief by sympathetic procaine block. Twenty-four of the 57 patients received sympathetic block with procaine, with varying amounts of relief of pain and sympathetic phenomena in all but two patients.

Treatment may be directed to blocking trigger points if they exist and to blocking the sympathetic pathway. In 12 patients treated by sympathetic procaine block alone, four had relief for one month to permanent, five who were followed less than one month had complete relief, one had 90 per cent relief for one month or over, one who was followed less than a month had 50 to 90 per cent relief, and the twelfth patient had temporary relief but refused sympathectomy.

Twenty-nine patients of the 57 here reported had sympathectomy performed, with complete relief of pain in 10 for one month to two years. One patient who had a follow-up less than one month had complete relief. Eleven patients had 50 to 90 per cent relief for periods ranging from one month to two and a fourth years. Seven patients had no, or but little, relief of pain.

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# SPONDYLOSIS AND SPONDYLARTHROSIS\*

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THE spine is a weight bearing structure and an instrument of motion. It resembles in this respect the joints of the lower extremities which likewise serve to bear weight and to carry out certain motions. There is, however, an important difference between the two. In the joints of the lower extremities the weight bearing surfaces are also the gliding surfaces for motion. In the spine the structures concerned with weight bearing are the intervertebral discs and the vertebral bodies while the motions are carried out in joints serving this purpose only. This necessitates a separate discussion of the disorders of the two functions.

## I. DISORDERS OF THE WEIGHT BEARING FUNCTION OF THE SPINE (SPONDYLOSIS)

The intervertebral disc undergoes definite changes in the course of life. The nuclear substance normally soft, like jelly, becomes gradually firm and dry due to a process of dehydration. Coincidentally the elastic elements of the disc are replaced with fibrous tissue just as is the case in the skin, lungs and arteries in the course of the aging process. As a consequence, there is a loss of elasticity so that the pressure of the trunk, amounting to a few hundred pounds when a weight is lifted, cannot be counterbalanced. Eventually, according to the experiments of Keyes and Comperes "minute ruptures of the cartilage plate" occur. This chain of events is called degeneration of the intervertebral disc. This process is regularly well distinguishable microscopically. In a certain percentage of cases, about 20 per cent in our experience, as an outcome of the process of degeneration, a thinning of the intervertebral disc results causing a narrowing of the intervertebral space which can be recognized radiographically (figure 4). In the final analysis this is due to the fact that the cartilage has no power of regeneration. Another reaction occurs instead. Just as the fracture of a bone stimulates the periosteum to develop a callus, so do the ruptures of the cartilage plates stimulate the adjacent vertebral bodies to produce new periosteal bone. The newly produced bone has the appearance of a marginal spur (exostosis, exophyt, lipping). The spurs are in the beginning only slightly pronounced, in later stages they are long, broad and variously curved. Large spurs of two adjacent vertebrae may join to form an osseous bridge spanning the intervertebral space. The spurs develop on the anterior surface and the lateral surfaces, occasionally also on the posterior surface (figures 1, 4, 5, 6, 10, 11).

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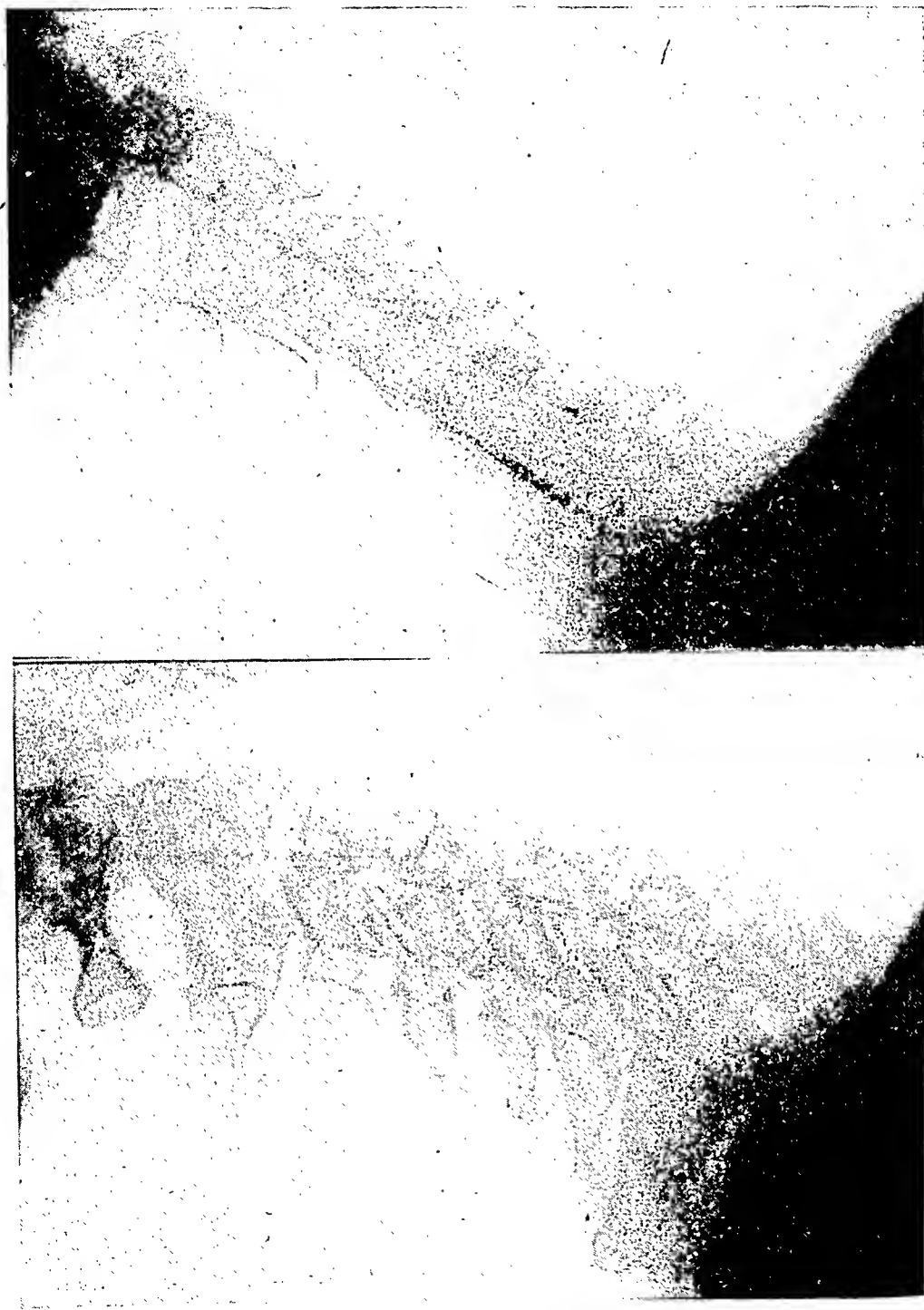


FIG. 1. (*Left*) Marginal spur on the anterior surface of the sixth cervical vertebra causing dysphagia due to its proximity to the esophagus. The apophyseal joints appear normal. Summary: spondylosis, no spondylarthritis.

FIG. 2. (*Right*) Osseous ankylosis of all apophyseal joints of the cervical spine. Summary: spondylarthritis, rheumatoid type, no spondylosis.

In the first year the rapidity of the growth of a spur varies considerably from individual to individual and from vertebra to vertebra. A normal appearing vertebra may develop a spur up to 1 cm. long within the first year. After the first year the growth continues at a very slow rate. Radiographic examinations usually reveal perceptible changes in the size of the spurs only at intervals exceeding two years.

The two most important factors controlling the growth of the spinal spurs are the body weight and the age.

The heavier the body weight, the earlier in life do the spurs become manifest. Willis found on cadavers that at the age of 45 only 10 per cent of the slender type but 83 per cent of the heavy showed hypertrophic spinal changes, most frequently in the lumbar spine. Furthermore, while at the age of 50 all cases of the heavy type showed marginal spurs, this condition resulted in the slender type at the age of 60 years.

As to the age factor, Feistmann-Lutterbeck found on roentgen-ray films of 1,250 persons the distribution of the marginal spurs as follows:

1%	in persons between 20 to 29 years of age
6%	in persons between 30 to 39 years of age
48%	in persons between 40 to 49 years of age
75%	in persons between 50 to 59 years of age
92%	in persons between 60 to 69 years of age
100%	in persons over 70 years of age

Summarizing, it appears that the marginal spurs are to be considered a reparatory reaction of the vertebral bodies to the degeneration of the intervertebral discs, progressing strictly in proportion to the age of the individual and hastened by the body type. In other words, as an answer to the flattening of the intervertebral disc, that is a diminution in the vertical direction, the marginal spurs tend—as Buckley put it—“to provide a wider articular surface” in the transverse and sagittal direction, and thus to restore the weight bearing capacity of the spinal column.

As to the clinical significance of the spinal spurs, there is a widespread inclination to hold them responsible for numerous clinical symptoms. Back-ache, stiffness, pain radiating from the trunk to the extremities, limitation of motion of the vertebral column are frequently considered the result of the lipping of the vertebral bodies. It is natural that we welcome the readily demonstrable, optically very impressive radiological findings in the vertebral bodies because they seem to give us a plausible cause for many complaints which otherwise would remain obscure.

Unfortunately, it is often very difficult to explain the causal connection between the changes seen on the roentgenograms of the spine and the clinical findings. The only instances in our experience, in which a marginal spur as such gave rise to clinical symptoms were cases in which large spurs located on the anterior surface of the cervical spine caused symptoms of dysphagia due to their close vicinity to the esophagus (figure 1). In an-



FIG. 3. Narrowing of the apophyseal joint between the fourth and fifth cervical vertebrae with subchondral osteosclerosis. Summary: spondylarthritis, osteoarthritic type, no spondylosis.

other group of cases reported in the literature, spurs growing into the spinal canal gave rise to neurological symptoms. Cases of this kind are exceptional. As a rule, the marginal spurs are not pathogenic. This is so in the first place because of the location of the spurs. How for instance can a spur on the anterior surface of a vertebra produce pain in an arm or leg since no peripheral nerves run in the front of the spine? Spurs are often seen on both sides of the spine while pain is felt on one side only. In other cases, pain is felt on one side while the spurs are present on the other.

There is, apart from the location of the spurs, another reason to doubt the causal connection between the radiological findings and the clinical symptoms. Were the symptoms the result of the spurs, they could never subside and would last permanently, unless the exostosis were removed surgically as is being done in the case of an exostosis of any other localization giving rise to clinical symptoms. Instead, we see that the symptoms for which the spurs are held responsible usually subside following physiotherapy or conservative orthopedic measures while the spurs remain as they were, and in due course of time even grow larger. This is evidence that the symptoms from which the patients suffered were not caused by the spurs but by other factors, such as myofibrositis, strained ligaments, diseases of internal organs, or true spondylarthritis which will be discussed later.

Another argument against the causal connection between the marginal spurs and the clinical symptoms commonly attributed to them is derived from the observation that roentgenograms of the spine of persons over 50 years taken shortly after an injury often reveal extensive lipping of the vertebral bodies which could not develop in the brief period between the injury and the roentgen-ray examination because this period amounts often only to a few days, sometimes merely to a few hours.

Last, not least, it is a common place experience that roentgenograms taken for diseases of the neck, chest or abdomen disclose numerous spinal exostoses while the patients do not have and never did have any complaints referable to the spine.

What has been said of the marginal spurs, fully applies also to the narrowing of the intervertebral space with which the spurs, in about 20 per cent, are associated. The flattening of the intervertebral disc in the course of the aging process is a painless process since no nerves are present in the discs (Jung and Brunschwig). Accordingly, even a highly pronounced narrowing of the intervertebral space by itself does not give rise to pain or any other symptoms.

The fact that the spinal exophytes and the flattening of the intervertebral disc are not pathogenic is in line with the previous statement that the marginal spurs rather than a pathological phenomenon are an adaptation of the intervertebral bodies to the physiological process of degeneration of the intervertebral disc.

There is an obvious analogy between the mode of the development and the appearance of the marginal spurs of the spine and those occurring in the

peripheral joints. The analogy is so far reaching that the condition has been called hypertrophic spondylarthritis or spondylarthritis deformans just as we speak of hypertrophic arthritis or arthritis deformans of the knees or hips. However, these terms have been criticized because as Oppenheimer has stated, "the articulation formed by two vertebral bodies and the inter-

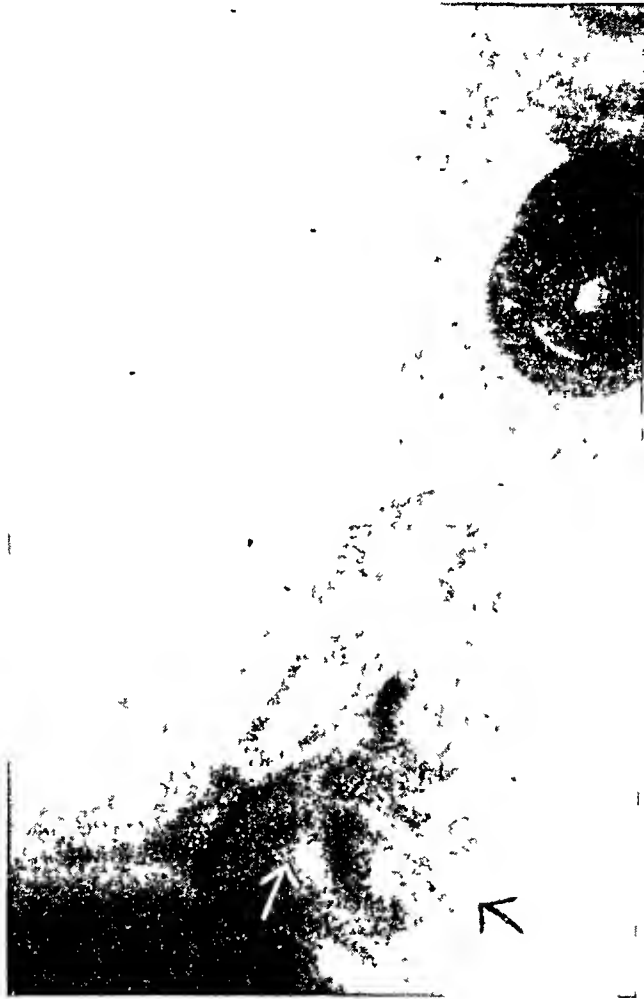


FIG. 4. Narrowing of the intervertebral space between the fifth and sixth cervical vertebrae with marginal spurs on the anterior surfaces of the respective vertebrae. The corresponding apophyseal joint is narrowed, the contours are indistinct. Summary: destructive spondylosis and spondylarthritis ("discogenetic" spondylarthritis).

vening discs is an amphiarthrosis or symphysis," and "since the vertebral symphyses have no synovial membranes, no joint cavities, nor free articular cartilages, nor any other parts characteristic of synovial joints, the symphyses cannot be the seat of arthritis. Accordingly, says George, the term hypertrophic spondylarthritis should not be used. It has no foundation of fact, it is not accurate and it has no pathological basis to substantiate its use." It may be added that the term hypertrophic spondylarthritis if used to in-

dicating the presence of marginal spurs, is a misnomer also for another reason. The reason is that the marginal spurs are not the result of an inflammatory process, but a reparatory reaction of the vertebral bodies to the degeneration of the intervertebral discs. Under these circumstances the term "hypertrophic spondylarthritis" or "spondylarthritis deformans" should not be applied with reference to marginal spurs, because they are bound to confuse the physicians as to the nature of the condition and its treatment, and to spread fear and anxiety among the patients.

For the last few years we have been using, for lack of anything better, the term spondylosis to designate the presence of abnormal findings in the weight bearing structures of the spinal column. We speak of marginal spondylosis if spurs are present at the edges of the vertebral bodies, and of destructive spondylosis if a narrowing of an intervertebral space also is present. It may be emphasized that a narrowing of an intervertebral space in absence of pronounced marginal spurs, is not characteristic of spondylosis but is rather suggestive of a protrusion of the nucleus pulposus if it occurs in the lower cervical or lower lumbar spine. It seems that the degeneration of a displaced disc takes place faster than of one in normal position so that the vertebral bodies are lagging in the production of new bone.

In a minority of the cases, approximately in about 10 per cent of the patients showing spinal spurs, these findings are not due to the aging process but due to other factors, such as deformities, injuries, infectious and neoplastic processes. The mechanism leading to the formation of the marginal spurs in these cases is basically not different from that in the process of disc degeneration due to the advancing age. As a rule, however, the spurs are limited to one area, and are often solitary. The roentgenograms which demonstrate the presence of the spurs in such cases usually also disclose the underlying pathological condition.

## II. DISORDERS OF THE MOTOR FUNCTION OF THE SPINE (SPONDYLARTHROSIS)

The intervertebral or apophyseal joints are the only true joints of the spine. They contain, as any joint of the extremities, a synovial membrane, two cartilaginous surfaces and a capillary space in which certain motions can be carried out. Radiographically the joint spaces appear as 1 to 2 mm. wide slits, sharply delineated by two parallel lines. The direction of the planes of the spinal joints is different in the various parts of the spine. In the cervical spine the joint spaces run in the anteroposterior direction and can be seen on lateral roentgenograms (figure 1). In the thoracic spine the joint spaces are turned in the frontal direction and can be visualized only on oblique views. In the lumbar spine the joint spaces are situated in the sagittal direction and can be seen both in the anteroposterior and oblique view. Of the two views the anteroposterior is less dependable because the planes of the lower lumbar vertebrae often instead of being situated sagittally

are turned more or less sideways. In addition, even a slight scoliosis or rotation of the spine changes the position of the intervertebral joints. Therefore, when a joint space in its full length cannot be traced on the anteroposterior roentgenogram, oblique views from varying angles should be taken (figures 6, 10).

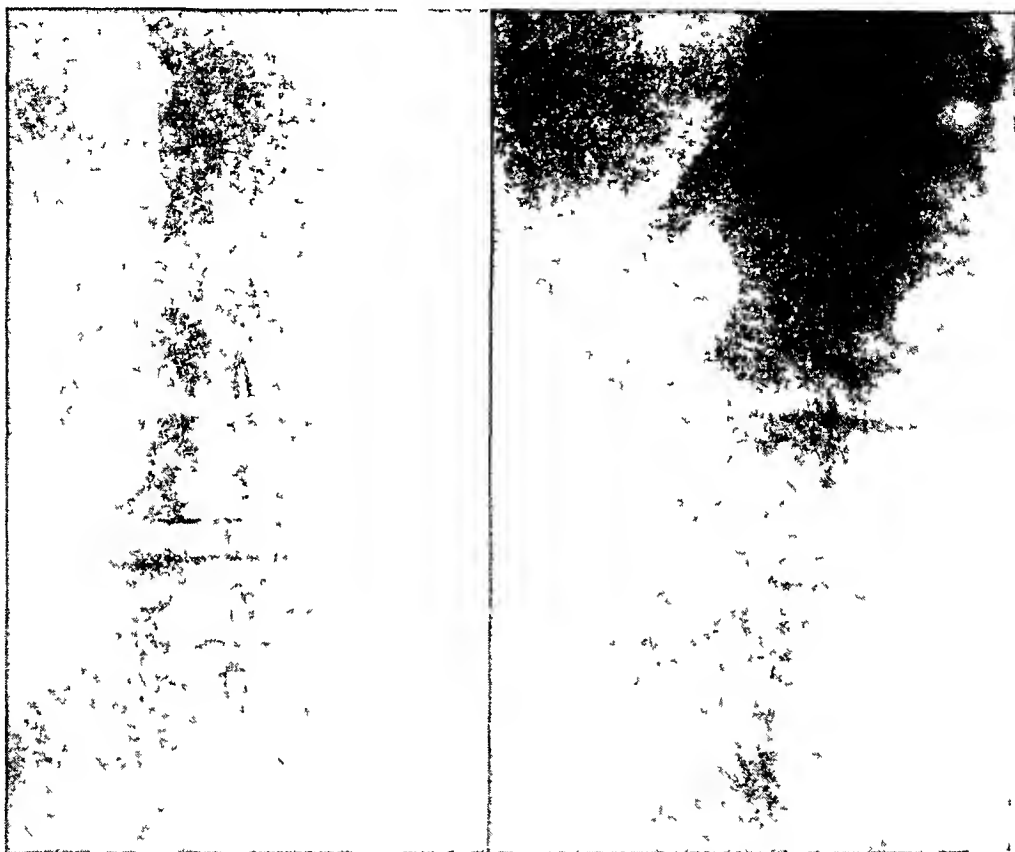


FIG. 5. (*Left*) Extensive marginal spurs in the lower lumbar spine.

FIG. 6. (*Right*) Same case as in figure 5. The apophyseal joints appear normal in the oblique view. Summary of figure 5 and figure 6: spondylosis, no spondylarthritis.

A true spondylarthritis can occur in the apophyseal joints, the only type of spondylarthritis unrestrictedly deserving this designation. Arthritis of any origin can develop. If we disregard the rare acute conditions caused by definite microorganisms, two main types of chronic spondylarthritis may be differentiated as they customarily are distinguished in the peripheral joints: the rheumatoid type and the osteoarthritic type.

Rheumatoid arthritis of the spine, also called Marie-Strümpell's spondylitis, predominantly affects young men. It is a systemic disease, which if not arrested, steadily progresses in the ascending direction until all intervertebral joints eventually show osseous ankylosis. Decalcification of the vertebral bodies and calcifications of the spinal ligaments are features accompanying the more advanced stages of the inflammatory process taking

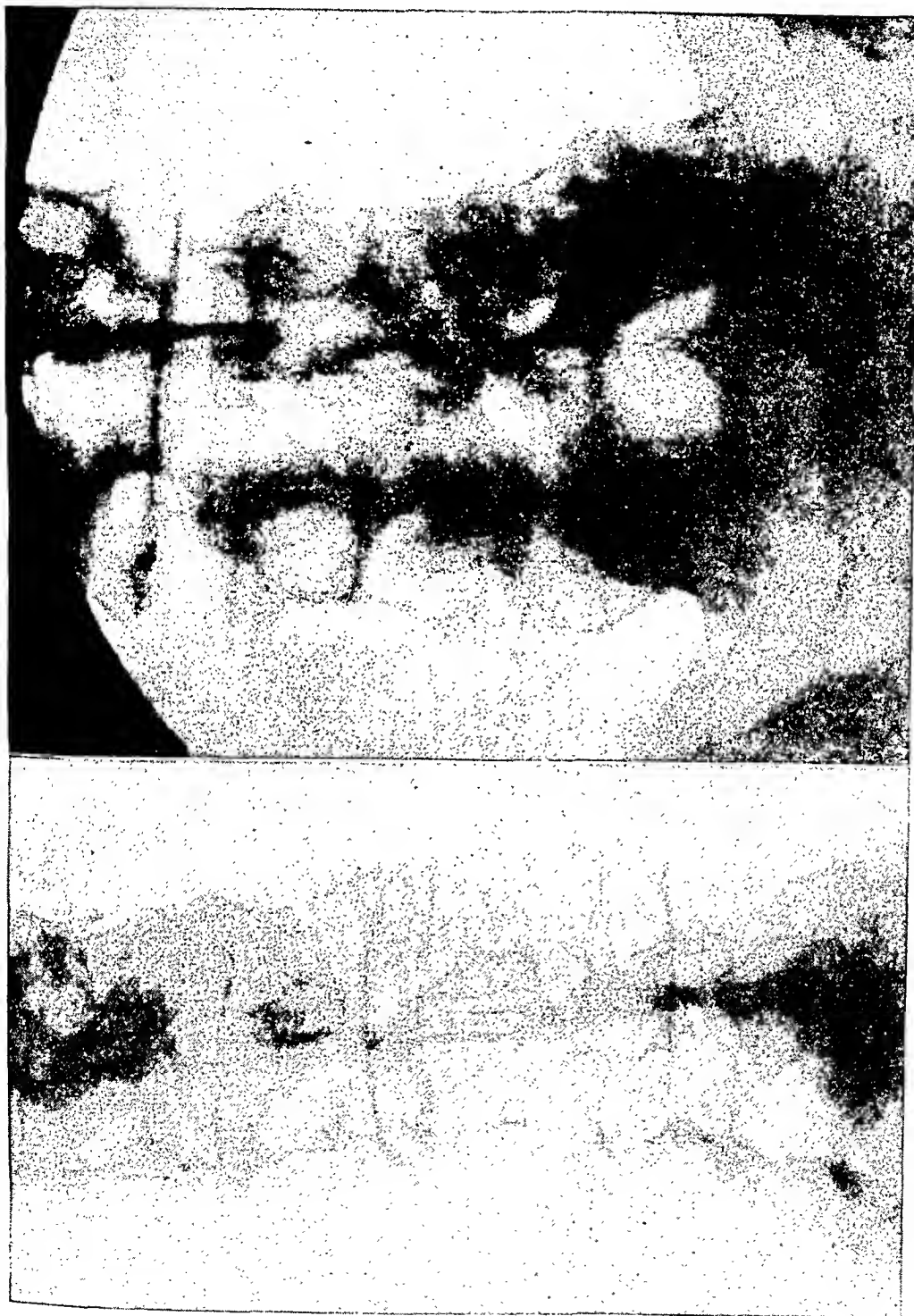


FIG. 7. (*Left*) Ankylosis of the apophyseal joints of the lumbar spine with beginning ossification of the corresponding spinal ligaments. Summary: spondylarthritis, rheumatoid type, no spondylosis.

FIG. 8. (*Right*) Condensation of the vertebral bodies of the lower lumbar spine around the apophyseal joints which appear narrowed.



place in the joints (figures 2, 7). The sedimentation rate of the red blood cells is, as a rule, increased.

Osteoarthritis of the spine is a disease of the middle and advanced age groups. It affects equally both sexes. It is a monoarthritic or oligoarthritic condition (figures 3, 9). The lower portions of the cervical, thoracic and lumbar regions of the spine are the sites of predilection. Osteoarthritis of the spine never causes an osseous ankylosis. The calcium content of the vertebrae is within normal range, except in very old individuals where it is reduced. The sedimentation rate of the red blood cells is normal.



FIG. 9. (Left) Same case as in figure 8 seen in an oblique view. The apophyseal joints are definitely narrowed and show subchondral bone sclerosis. Summary of figures 8 and 9: spondylarthritis of the osteoarthritic type, no spondylosis

FIG. 10. (Right) The upper three lumbar vertebrae with signs of marginal spondylosis. The intervertebral spaces and the apophyseal joints appear of normal width.

As to the local symptoms, swelling of the joints, a finding so valuable in the diagnosis of arthritic conditions of other localizations, cannot be noticed in the spine because the joints are covered by many layers of thick muscles. In both types of spondylarthritis there is backache, limitation of motion, pain radiating into the limbs, and tenderness on pressure to one side or both sides of a spinous process, corresponding to the joints affected. Radiographically, osseous ankylosis is characteristic of rheumatoid arthritis, marginal spurs, sharpening and thinning of the facets of osteoarthritis. Otherwise, the differences between the two types are not very pronounced. In both types the lumen can be narrowed to the point of its indiscernibility. The contours are blurred, often ragged and wavy. The subchondral bone is porotic in the initial stages and condensed in the later stages. The condensation may reach the stage of heavy sclerosis (figures 2, 3, 4, 7, 8, 9, 11).

## III. RELATIONSHIP BETWEEN SPONDYLOSIS AND SPONDYLARTHRTIS

As to the relationship between spondylosis and spondylarthrtis, things are different in the two types of chronic arthritis of the apophyseal joints. No marginal spurs or narrowing of the intervertebral spaces occur in the rheumatoid type of spondylarthrtis since the latter is a disease of young adults and no degenerative changes take place in the intervertebral discs at



FIG. 11. Same case as in figure 10 seen three years later. There is an increase of the marginal spurs. The intervertebral spaces and the apophyseal joints appear narrowed, the bone around the joints is condensed. Summary of figures 10 and 11: with the establishment of the destructive spondylosis signs of spondylarthrtis, osteoarthritic type, develop ("discogenetic" spondylarthrtis).

that age. Only when the patients reach the age at which the spurs normally develop, do they exhibit in addition to their spondylarthrtis also signs of spondylosis. This indicates that even a highly pathologic process of the apophyseal joints as it occurs in rheumatoid spondylarthrtis does not in any way accelerate the process of degeneration in the intervertebral discs. One is time and again surprised to see that even spines of the "bamboo" type showing osseous ankylosis of all spinal joints and complete ossification of the spinal ligaments show no marginal spurs and normal intervertebral spaces.

The contrary is true of osteoarthritis. Out of 43 cases with radiological signs of osteoarthritis only eight, thus about 20 per cent, showed no signs of spondylosis. Thus the vast majority of the patients afflicted with osteospondylarthritis also showed signs of spondylosis. This frequent coexistence suggests the possibility that spondylosis may be a factor in the development of spondylarthritis.

To clarify this problem we examined 92 cases showing marginal spondylosis, that is spurs without narrowing of an intervertebral space. Twenty-four patients of this group showed also radiological signs of osteospondylarthritis. Thus spondylosis was considerably more frequent than spondylarthritis. Only about 25 per cent of the patients with marginal spondylosis had also signs of osteoarthritis of the apophyseal joints. This ratio does not suggest that spondylosis favors the development of spondylarthritis, the more so since the site of the spondylosis often did not coincide with the site of the spondylarthritis. The coincidence of the two conditions in a certain percentage of cases is only natural in view of the fact that both occur in the middle and advanced age groups.

The ratio between spondylosis and spondylarthritis changes distinctly when we limit our attention to the cases with signs of destructive spondylosis, thus showing not only marginal spurs but also a narrowing of an intervertebral joint. Out of 23 cases of this type, 11, thus about 47 per cent, also showed signs of osteospondylarthritis. This is nearly twice the incidence found among the cases with marginal spondylosis. The occurrence of osteospondylarthritis is in this group even more frequent when we include cases without radiographic evidence of a joint disease which, however, had the clinical symptoms of osteospondylarthritis comparable to synovitis in the peripheral joints. In the course of the observation of such patients, we have seen cases which on the first examination were roentgenographically negative but turned out roentgen-ray positive some time later (figures 10, 11). It seems probable that the majority of the patients with a narrowing of an intervertebral space are likely, sooner or latter, to develop osteoarthritis of the apophyseal joints. This is in line with observations of Williams, Ayers and Oppenheimer.

The explanation of the connection between destructive spondylosis and osteospondylarthritis runs along the following line: when the degeneration of an intervertebral disc has advanced to a degree producing a narrowing of the intervertebral space, then the superior articular processus slips downwards and the congruence between the articulating facets of the apophyseal joints is lost. A state of irritation results which gradually leads to changes in the intervertebral joints, both in the synovia and the cartilage, causing backache and pain on moving the joints. The frequency of radiating pain is due to the proximity of the intervertebral joints and the intervertebral foramina which are traversed by the spinal nerves on their way to the limbs.

Thus, besides the idiopathic cases of osteospondylarthritis, in which the origin of the disease is as obscure as in osteoarthritis of many other localiza-

tions, there is a group of cases of "discogenetic" origin, to employ the terminology of Oppenheimer (figures 4, 11).

Summarizing, the connection between spondylosis and spondylarthrosis may be explained as follows. Originally, spondylosis is an adaption of the vertebral bodies to the degenerative processes in the intervertebral discs. Spondylosis is not pathogenic nor arthrogenic as long as spurs are its only manifestation. In about 20 per cent of the cases the degeneration of the disc advances to a degree causing a narrowing of an intervertebral space. Once this stage is reached, spondylosis becomes a condition predisposing to spondylarthrosis, or, as may be said, a prearthritic condition which, sooner or later, is likely to lead to the development of an osteoarthritis of the intervertebral joints.

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# CASE REPORTS

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## MALIGNANT THYMOMA IN A CASE OF MYASTHENIA GRAVIS \*

By SAMUEL E. MILLER, Lt. Col., M.C., A.U.S., and WALTER REDISCH, Capt., M.C., A.U.S.

A case of myasthenia gravis occurring in a 21 year old soldier with a mediastinal mass which proved to be a malignant tumor arising from the thymus gland is reported. The reasons for reporting a single case are: the interesting but still poorly understood relationship existing between thymic tumors and myasthenia gravis; the fact that in the vast majority of cases, these tumors are non-malignant; and because of its military medical aspect in that any case of abnormal fatigability occurring in a soldier requires consideration of myasthenia gravis as a possible cause.

### CASE REPORT

A 21 year old white male soldier with one year of service was admitted to the hospital October 17, 1944 from his regimental dispensary. His first symptoms appeared during basic training. While doing manual of arms he noticed that his wrists gave out and he was unable to extend his arms. After he had rested for a while he was able to resume his activity. On his first march, after going a mile or two, his knees buckled and he had to sit down. After resting he was again able to proceed for a short while. He also noticed that on awakening in the morning he felt well, but became progressively more tired as the day passed. After two months of basic training, which he was unable to complete because of this weakness, he was sent to radio school. He had no great difficulty there because of the sedentary nature of the work. Two months later, upon completion of his course, he was returned to duty with his organization. The same symptoms promptly recurred. He was then placed on limited service and excused from arduous duties.

Early in October, 1944 he noticed that liquids and foods leaked out of his mouth toward the end of a meal. He also noticed that after talking for several minutes his speech became slurred and indistinct. Toward the end of the day he would notice diplopia.

Physical examination on admission revealed incomplete bilateral ptosis, profuse collection of saliva in mouth, and slurring of speech of fatigue type. Laboratory studies, including urinalysis, complete blood count, serology, glucose tolerance, basal metabolic rate, and stool examination for parasites and ova, were all negative. Chest roentgenogram revealed a marginated shadow of homogenous density in the anterior superior mediastinum, measuring about two inches vertically and one and one-half inches horizontally, with compression of adjacent lung tissue. Fluoroscopy revealed the mass to be pyramidal in shape, and not to pulsate or move on swallowing. The impression was a thymic tumor.

Upon examination the soldier was believed to have myasthenia gravis. Alleviation and aggravation tests, using prostigmine and quinine, respectively, were both

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strikingly positive. When given 10 grains of quinine by mouth the following phenomenon took place: About 30 minutes after medication he suddenly became very weak, his speech unintelligible, he was unable to swallow water, and he could not sit up. This was relieved promptly by injection of 1 c.c. of 1-2,000 prostigmine methylsulfate. For therapeusis he was administered 1 c.c. of 1-2,000 prostigmine methylsulfate hypodermically before meals with complete alleviation of symptoms. This enabled him to eat his meals without difficulty. His speech became clear and articulate within 15 to 20 minutes after injection. Although his symptoms showed progression during his hospital stay, especially in his facial mimic and deglutition muscle groups, increased doses of prostigmine were able to compensate.

Because of reports of similar cases in which removal of thymic tumors had resulted in marked improvement of the clinical picture of myasthenia gravis, he was transferred to a thoracic surgery center November 28, 1944 for consideration of operation. After his transfer the medication had to be increased to 1 c.c. of 1-2,000 prostigmine methylsulfate every three hours. The indication for operation was concurred in at the thoracic surgery center and an operation was performed December 9, 1944. A median sternotomy was performed and a firm, lobulated tumor occupying the region of the anterior mediastinal space and extending both to the right and to the left and up into the neck was found. No definite capsule was present, except in a few areas, and the tumor appeared to invade most of the adjacent structures. Three large parts were removed separately but the mass in the right lateral region was left in place as it was obvious that the tumor was malignant and could not be totally removed.

Immediately after operation the patient's condition was good but great difficulty was encountered in keeping the tracheobronchial tree clear of secretions. Frequent aspirations were necessary. On the evening of the third postoperative day breathing became very difficult and the patient died.

The essential findings on autopsy were: an apparently malignant tumor of the thymus gland which infiltrated the pericardium; atelectasis of the left lower lobe due to bronchial obstruction from mucus; and cerebral edema.

The clinical diagnosis of myasthenia gravis was borne out by histological findings. Microphotographs 1 to 5 illustrate the histopathology of the tumor and of the striated muscle lesions.

### DISCUSSION

Since Laquer and Weigert<sup>1</sup> first called attention to a suspected relationship between thymic hyperplasia and myasthenia gravis in 1901 much interest has been shown in developing a better knowledge of this syndrome. The assumption that the presence of thymic pathologic lesions in connection with clinical myasthenia gravis may be more than a mere coincidence seems to be supported by the following facts:

1. According to literature,<sup>2,3,4</sup> 50 to 80 per cent of all cases of myasthenia gravis coming to necropsy have shown pathologic changes in the thymus varying from simple hyperplasia to true tumors. These tumors of the thymus, as described in the literature, have practically always been benign.<sup>5,6</sup> The first case in which a malignant thymic tumor was described in connection with myasthenia gravis was published in 1908.<sup>7</sup> Since that date, however, in one series of 95 cases,<sup>8</sup> six were reported as having malignant thymomas. One authority on the subject<sup>9</sup> has expressed the opinion that the association of malignancy of the thymus gland and of myasthenia gravis is not as rare as it is thought to be.

2. Two investigators in 1945 found the incidence of myasthenia gravis in cases of thymoma to be nearly 100 per cent.<sup>10</sup>

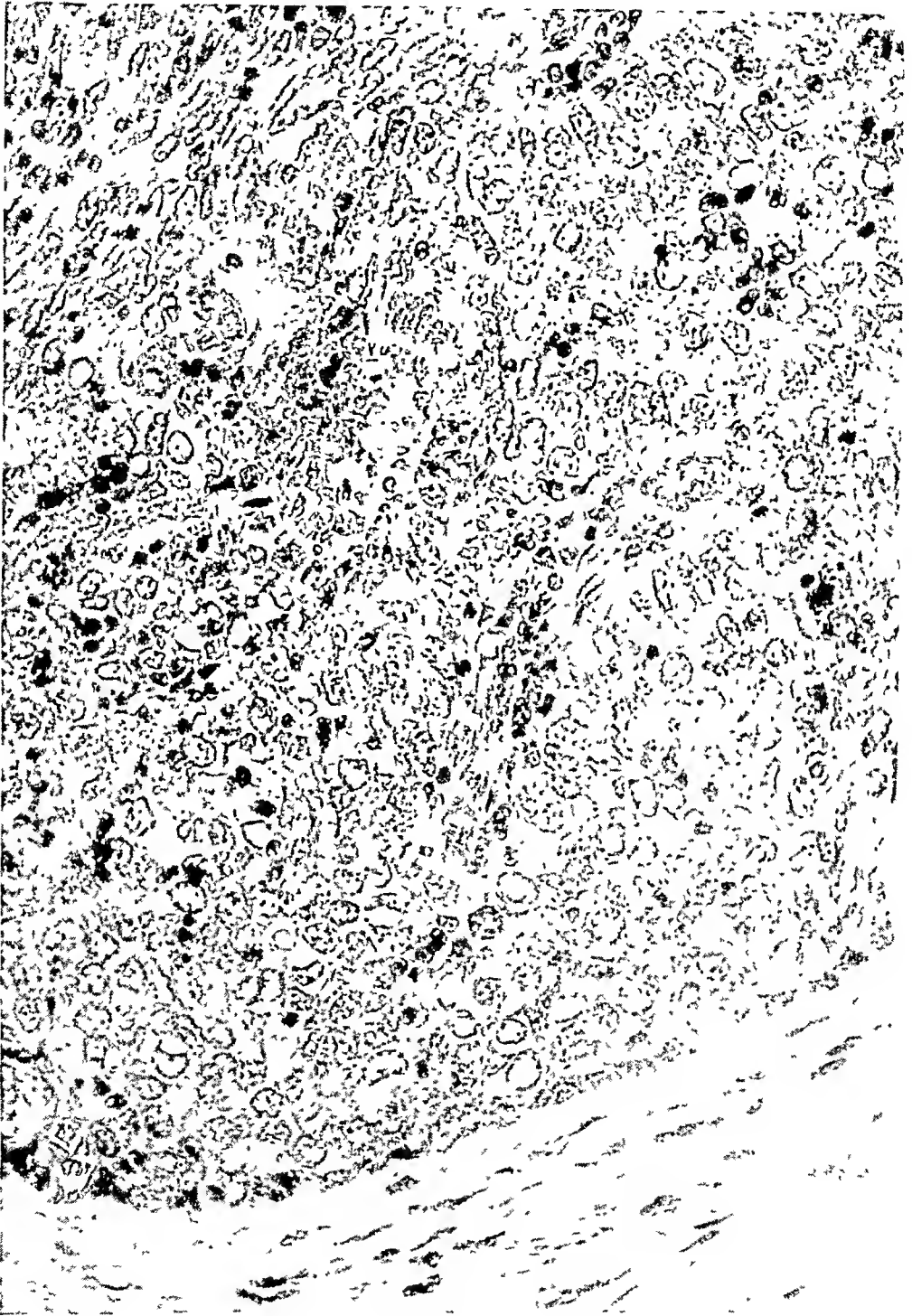


FIG. 1. Section through the primary malignant thymic tumor. Most of the cells in this section are large polygonal cells with pale vesicular nuclei. In some places they are hyperchromatic and spindle-shaped. These cells tend to assume a palisade arrangement. Occasional mitotic figures can be seen. Scattered cells resembling "lymphocytes" (thymocytes) are seen throughout the section. No form of differentiation to Hassell's corpuscles can be discerned. This portion of the tumor shows what appears to be a capsule. U. S. Army Medical Museum Negative No. 88069.



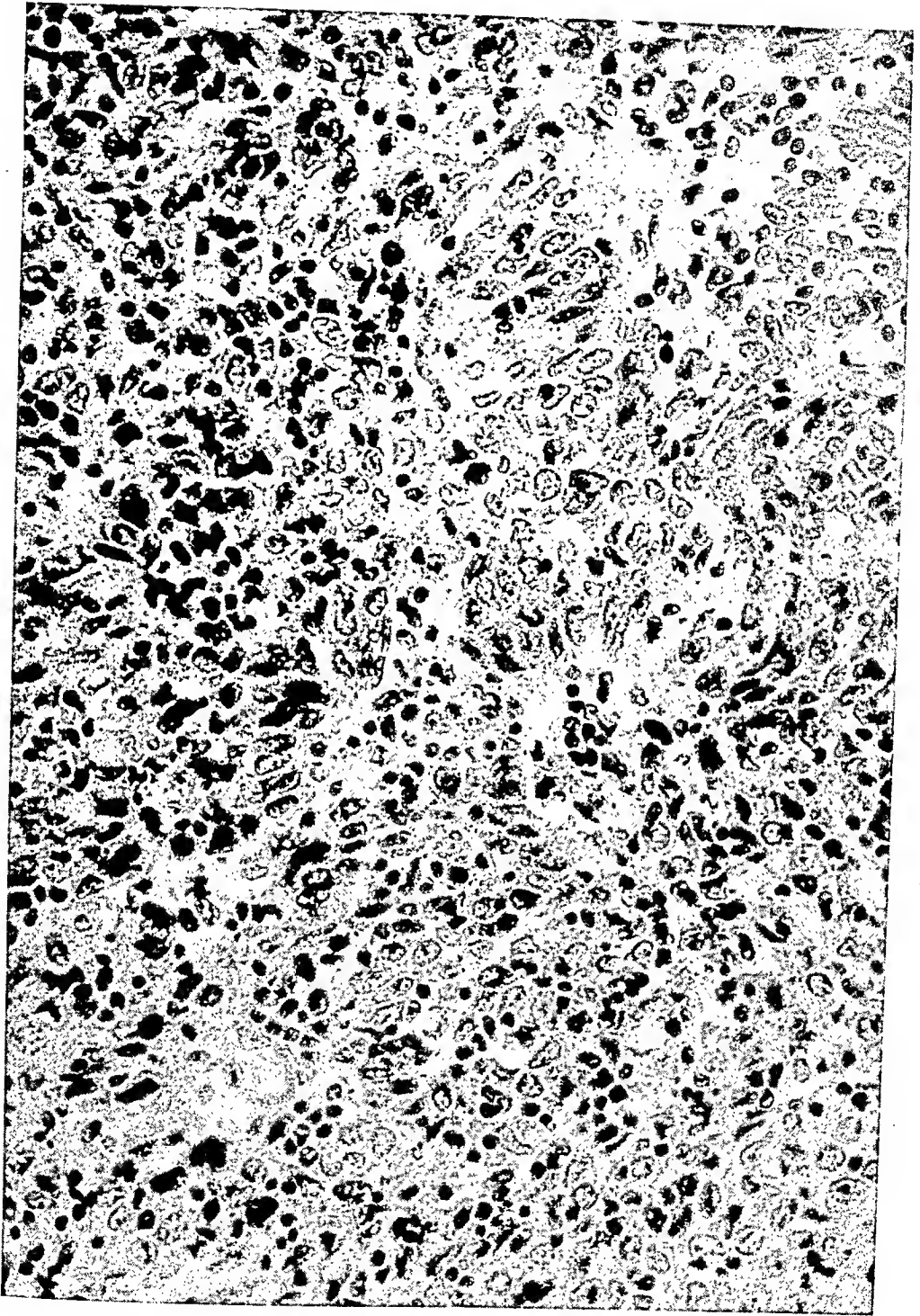


FIG. 2. Section through the tumor which is very similar to figure 1. The tendency to palisade arrangement of the hyperchromatic cells is more marked. U. S. Army Medical Museum Negative No. 88072.



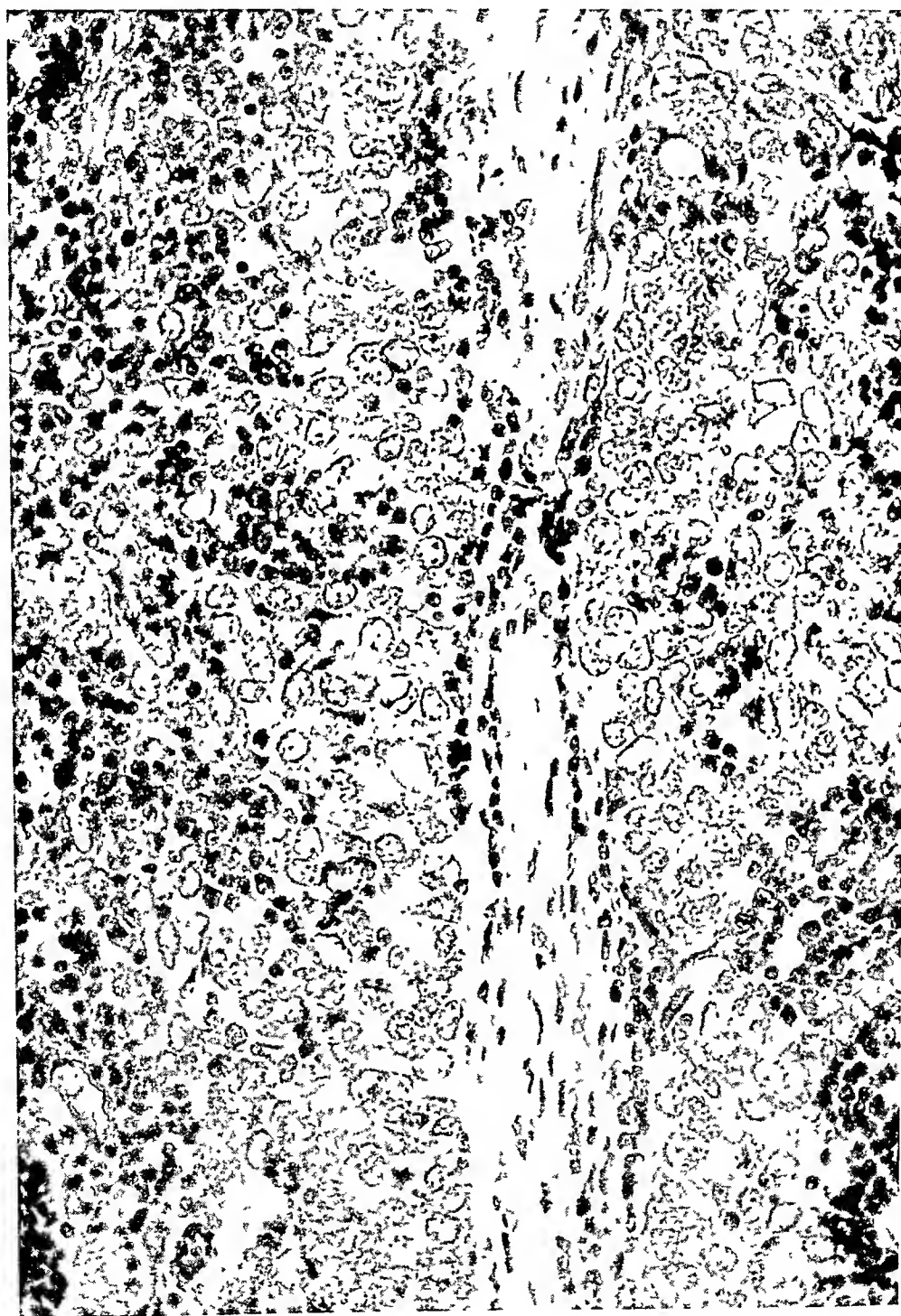


FIG. 3. Section through tumor showing small thymocytes which are more numerous in this section than in the others. The tumor cells are almost all of the large, pale, vesicular type and closely resemble reticulum cells. No palisade arrangement and no structures resembling Hassell's corpuscles can be discerned. U. S. Army Medical Museum Negative No. 88071.



FIG. 4. Section of skeletal muscle showing very large, dense focus of lymphorrhagia. Such lymphorages are characteristic lesions of myasthenia gravis. U. S. Army Medical Museum Negative No. 88073.



FIG. 5. Perivascular collection of lymphocytes in skeletal muscle. U. S. Army Medical Museum Negative No. 88068.

3. The relationship is further supported by therapeutic results achieved through thymectomy in cases of myasthenia gravis. Since the first such attempt in 1913,<sup>11</sup> several such reports have appeared all over the world. In this country there are reported several instances in which myasthenia has been alleviated by thymectomy.<sup>12, 13</sup> Although results have not been completely successful and the possibility of spontaneous remissions has to be considered, the over-all evidence seems to be in favor of operation whenever a definite thymic tumor can be demonstrated.

4. The syndrome has been produced experimentally by repeated implantation of infantile thymus into dogs. The resulting picture of myasthenia gravis was then alleviated by the administration of prostigmine.<sup>14</sup>

Discussion of the physiology of the mechanism involved and of the aspects of modern therapy appears unnecessary here as it has recently been excellently presented.<sup>13</sup>

From a military standpoint this is a case which illustrates the necessity for proper consideration and evaluation of subjective complaints. Failure to do so might result in the unfortunate labeling of a sick man as a "goldbrick." It appears that two factors may have contributed to failure of early recognition of this man's condition: (1) Insufficient attention was paid to his subjective complaints; and (2) the rather innocuous early symptoms, that is abnormal muscle fatigability with obvious recovery on rest, were not properly evaluated.

### SUMMARY

1. A case of myasthenia gravis with malignant tumor of the thymus is reported.
2. The relationship between pathologic lesions of the thymus and the clinical picture of myasthenia gravis is discussed.
3. The military medical aspect of the case is considered.

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## PRIMARY AMYLOIDOSIS: REPORT OF A CASE \*

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ONLY in recent years has there been some unanimity of opinion in regard to the classification of amyloid disease which is divided into primary amyloidosis, secondary amyloidosis, amyloid associated with multiple myelomata and tumor-like formation.

Primary amyloidosis is subdivided into the systemic and localized types in which some variation occurs. It was first described in 1856 by Wilks,<sup>1</sup> but is still poorly understood, and of unknown etiology. In 1936 Kerwin<sup>2</sup> reported two cases and in 1939 Koletsky and Stecher<sup>3</sup> made a comprehensive review of the literature noting some 30 cases, 22 of which were of the systemic type. They also added one of their own. Their series did not include the case of Larsen<sup>4</sup> or that of Budd,<sup>5</sup> nor the two cases reported by Kerwin.<sup>2</sup> Since then single cases have been reported by Binford,<sup>6</sup> and by Sappington, Davie and Horneff.<sup>7</sup> Pearson, Rice and Dickens<sup>8</sup> have reported two cases and Dillon and Evans<sup>9</sup> three cases, making a total of 44 cases.

Considerable emphasis has been placed on the tendency of primary amyloidosis to involve the mesodermal tissues, especially the skeletal and smooth muscles of the cardiovascular and gastrointestinal system, whereas in the secondary type, the liver and spleen are chiefly involved. Importance has also been attributed to the atypical staining in the primary form in contrast to the uniform staining in the secondary type, which suggests that the two types are not chemically identical.

The Bennhold Congo red test when completely positive is practically pathognomonic of this disease. If the possible presence of amyloidosis is kept in mind, the clinical findings, which have been more fully described in recent years, should suggest the diagnosis. The verified presence of amyloidosis is important from the point of view of prognosis.

### CASE REPORT

W. A. J., a 58 year old male, on January 31, 1942 complained of swelling of the ankles for about three months. The family history was irrelevant. He had had measles, mumps, chicken pox and typhoid fever. His general health, however, had been excellent; and he had not experienced any operations or injuries. He worked in the printing department of a large firm but did not come in contact with lead. There was contact with cleaning fluid frequently. He was a total abstainer from

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alcohol and tobacco. In the present illness there were no symptoms referable to the circulatory system except edema of the ankles. The respiratory system was negative. His appetite was poor owing to slight digestive upsets at times. There were no symptoms of urinary tract disease, except for the discovery of albumin in the urine two months before admission.

On physical examination the important findings were as follows: Ears were negative. The pupils reacted normally and there was no icterus of the conjunctivae. In the ophthalmoscopic examination a patch of choroiditis was noted in the right eye near the disc. The examination of the nose, teeth, tonsils, tongue, and neck was negative. Lungs were clear. The cardiac dullness extended 8 cm. to the left of the mid-line in the fifth interspace. No shock or thrill was palpated. The cardiac rate was 115; and the rhythm regular. No murmurs were heard. There were no prominent veins on the abdomen. The liver edge extended two fingers' breadth below the costal margin and liver dullness was 5 cm. below it in the mid-clavicular line. The edge was sharp and smooth and there was no tenderness. Splenic dullness was increased and the spleen was easily palpable and thought to be moderately enlarged. The kidney regions were negative on palpation. The upper extremities were negative. In the lower extremities there was pitting over the tibia of both legs. Veins were slightly prominent. Reflexes were normal. The genitalia were negative. There was pitting over the lower lumbar and sacral regions, posteriorly. Height 5' 5½"; weight 155½ lbs.; temperature 98.2°; blood pressure, systolic 94, diastolic 74.

The laboratory findings were as follows: Hemoglobin 13 gm., red blood cells 4,510,000; white blood cells 6,400; differential count, polymorphonuclears 67 per cent, lymphocytes 35 per cent, monocytes 3 per cent, basophiles 1 per cent. The cells were normal in size and shape and a few platelets were present. The blood did not coagulate readily. Sedimentation rate: First 15 minutes 25 mm., one-half hour 41 mm., 45 minutes 50 mm., one hour 51 mm. (corrected 46 mm.) (Wintrobe). Blood sugar, two hours after breakfast, was 106 mg. per 100 c.c. Urine was dark amber, specific gravity 1.028, alkaline, pH-6, negative sugar, four plus albumin. Microscopically there was an occasional pus cell, a few casts and few phosphate crystals. Kline exclusive test for syphilis: negative.

Fluoroscopic examination of the chest: Apices and lung fields were clear. The hilus shadows were slightly increased on the right. Diaphragm action was normal. The heart and aortic shadows were within limits of normal.

Electrocardiographic findings: Auricular and ventricular rate 105; rhythm regular; PR interval 0.16 sec.; QRS duration 0.04 sec.; voltage, total in 3 limb leads 11 mm.; slight slurring of QRS complex in Leads I, II and notching in Lead III; ST segments isoelectric; T<sub>1</sub> upright and normal, T<sub>2</sub> upright and slightly low, T<sub>3</sub> slightly inverted, T<sub>4</sub> upright and normal.

On February 3, 1942, he was sent to the Columbia Hospital for further laboratory studies which were as follows: Blood urea 29.98 mg. per 100 c.c.; prothrombin time 40 sec. (Quick); coagulation time 4 min.; bleeding time 8½ min.; blood platelets 300,000; serum albumin-globulin ratio: albumin 3.6 per cent, globulin .9 per cent, total proteins 4.5 per cent. This was repeated eight days later and the albumin was 3.8 per cent, globulin 0.9 per cent, total 4.8 per cent. Sedimentation rate: first 15 min. 40 mm.; 30 min. 46 mm.; 60 min. 52 mm. The urine was acid, specific gravity 1.002, three plus albumin, negative sugar, occasional granular cast, a few pus cells, a few epithelial cells. Quantitative albumin was three grams per liter. Urine was negative for bile. An intravenous phthalein test showed 44 per cent output in the first 20 min., and 18 per cent in the next 20 min. The following blood pressure readings were made: February 4: systolic 110, diastolic 74; February 6, 112/72; February 8, 110/68; February 9, 110/62; February 11, 108/70; and February 14, 110/64. Impression at this time was a tubular nephritis and possibly an early cirrhosis of the liver. During



his stay in the hospital he was placed on a high protein, salt free diet, and given Lextron and amino acids. He left the hospital on February 16. The edema had diminished considerably and he felt stronger.

On March 6, 1942 he became mentally upset, had a slight chill and fever of 100.3° F. He returned to the hospital for 10 days. The fever lasted only three days and he soon became rational again. The blood pressure remained about systolic 110 and diastolic 72. The liver was still palpable two fingers' breadth below the costal margin and the spleen was also palpable. The edema was practically gone. Laboratory studies showed a hemoglobin of 80 per cent, white blood cells 11,000, polymorphonuclears 84 per cent, lymphocytes 15 per cent, L mononuclears 11 per cent. Blood urea was 49.96 mg. per 100 c.c. Urine was acid, specific gravity 1.018, one plus albumin, negative sugar, occasional pus cell and occasional granular cast. He was dismissed on March 16. The diagnosis remained the same.

After returning home he continued to improve to some extent. The Lextron was kept up and multiple vitamins added. The edema varied. Theobromine sodium salicylate was used without much success and later the edema became so marked that he was again admitted to the hospital on August 10, 1942. There was some ascites present but no enlarged veins on the abdomen. The liver was three fingers' breadth below the costal margin, easily palpable. The lower extremities were moderately edematous. Several blood pressure readings were made which averaged systolic 110 and diastolic 73. Laboratory studies at this time were as follows: Hemoglobin 80 per cent, white blood cells 14,000, polymorphonuclears 74 per cent, lymphocytes 26 per cent. Blood urea was 34.96 mg. per 100 c.c. Urine was acid, specific gravity 1.010, albumin 4 plus, negative sugar, occasional waxy cast, occasional blood cell, few pus cells. Blood protein could not be determined on account of the milky appearance of the serum. Unfortunately, lipoids could not be determined. He was now placed on a diet of protein 110 gm., fat 50 gm., carbohydrate 200 gm., and salt free. Digitonin was given for a short period of time. Ammonium chloride 90 grains a day was given for three days, followed by salyrgan-theophylline 1 c.c. The salyrgan was given from then on every four days with ammonium chloride the day before and the day of each dose until the edema cleared. He left the hospital on September 7. Improvement continued at home, and he was able to walk short distances.

One month later he was sent to Johns Hopkins Hospital with the diagnosis of nephrosis, probably lipoid, and an unexplained enlargement of the liver and spleen. He was admitted on October 5, 1942 on the service of Dr. Louis Hamman. The laboratory studies were interesting and were as follows: Oct. 6, 1942, Serologic tests for syphilis in the blood: Flocculation test negative; blood slide test negative. Blood count: Red blood cells 5,130,000; hemoglobin 15 gm. (103 per cent), volume of packed red cells 41.7 per cent. White blood cells 7,150; volume of packed white cells 0.9 per cent. Sedimentation rate 49.0 mm. 1 hr., corr. 39.0 min.; icterus index could not be read. Mean corpuscular volume 81, mean corpuscular hemoglobin 29, mean corpuscular hemoglobin concentration 36, moderate anisocytosis. Differential count: Segmented neutrophils 85 per cent, eosinophils 2 per cent, basophils 1 per cent, lymphocytes 4 per cent, monocytes 8 per cent. Blood analysis: serum non-protein nitrogen 30 mg. per cent, globulin 2 gm. per cent. Stool examination: Occult blood (Guaiac), Oct. 8, 1942: 3+. Total protein in urine in 24 hours 11 gm.; basal metabolism -3 per cent. Test satisfactory. Oct. 9, 1942: Stool examination: Occult blood (Guaiac) +. Bromsulfalein retention: serum too cloudy to read, probably a trace of retention. Blood analysis: non-protein nitrogen 40 mg. per cent, blood urea nitrogen 24 mg. per cent, urea clearance No. 1, 39 per cent normal standard clearance; urea clearance No. 2, 38 per cent normal standard clearance. Oct. 10, 1942: Fishberg concentration test: 1.022 (7 a.m.), 1.020 (8 a.m.), 1.015 (9 a.m.). Stool examination: No gross blood or pus present. Occult blood (Guaiac) ++.

Search for parasites fruitless. Urine: Dark-field examination of centrifuged specimen showed no doubly refractile bodies. Stool culture: No typhoid-dysentery group found. Oct. 12, 1942: Phenolsulfonphthalein excretion: one-half hour, 30 per cent; one hour, 10 per cent; two hours, 10 per cent: total, 50 per cent. Prothrombin time: Patient, 13 seconds. Normal control, 14 seconds. Blood analysis: Calcium 8.4 mg. per cent, phosphorus 3.8 mg. per cent. Refraction index too cloudy to read. Hippuric acid test: 1.68 grams hippuric acid excreted over 1 hr. period. Normal: 1.0 to 1.4 grams. Vitamin A determination: Carotene, .25 mg. per cent, A, 1.72 L.U.  $\times 10^3$ , Normal: 1.48 — 3.30 L.U.  $\times 10^3$ . Oct. 13, 1942: Cholesterol: total 449 mg. per cent, esters 322 mg. per cent. Oct. 14, 1942: Platelets 230,000. Smear also showed platelets normal in number. Oct. 5, 1942: Urine analysis: 1.015, clear alkaline reaction, no sugar, albumin + + + +, Slight sediment containing an occasional white blood cell, no red cells. A few hyaline and waxy casts. Oct. 12, 1942: Sulkowitch test negative. Oct. 13, 1942: Clotting time 11 minutes.

There were several consultations and on Oct. 10, 1942 Dr. J. E. Howard made the following notation: "anasarca, albuminuria, excessive without red blood cells and with only few casts, marked hypoproteinemia with altered A/G ratio, greatly elevated blood fat—all point to nephrotic syndrome. Why the enlarged liver and spleen? Could the hypercholesterolemia induce by necessity xanthomatous changes in liver and spleen? Probably anything that will produce low serum proteins with albuminuria would raise the cholesterol. I don't know the answers to these questions but believe most likely is chronic glomerular nephritis in nephrotic phase. Amyloid, xanthomatosis, lymphoma seem far less likely. Dr. Fleischmann will do fractionated cholesterol for us." Oct. 9, 1942 Dr. Longcope wrote: "There is still very marked anasarca, edema of conjunctivae, of the scrotum and of the penis. His color is a remarkable pallor without the slightest yellow tinge, and yet he apparently has no anemia. There are several purpuric subcutaneous hemorrhages, particularly where he has been stuck with needles. No bleeding from gums or nose. Other striking features are edema of retina, patch of choroiditis on the right, rather small area of cardiac dullness without changes in sounds; extensive dullness and suppression of breath sounds at both bases posteriorly, ascites and readily palpable liver and spleen without noticeable enlargement of superficial veins over abdomen without bruits in the epigastrium; low blood pressure and comparative comfort. I think he has not only degenerative disease of the kidneys but of the liver, the etiology of which is, of course, completely obscure. Although amyloid disease is possible it is certainly not probable." He was discharged on Oct. 14, 1942 and the following day Dr. Hamman wrote me his impression which was as follows: "There can be no doubt that Mr. J. has chronic nephritis of the so-called nephrotic type. I never have seen an instance with as profound a disturbance of fat metabolism. The amount of fat in the blood is astonishing and the cholesterol in the blood is in the neighborhood of 600 mg. per 100 c.c. Some of the men in the laboratory are working on the fat and I hope later they may be able to give us the proportion of cholesterol in the form of esters. This has no practical importance but is an interesting detail. As a rule these cases in adults gradually go on to the development of renal function impairment with hypertension and later elevation of the non-protein nitrogen of the blood. In Mr. J. this stage has not been reached for his blood pressure is at a normal level as is also the non-protein nitrogen of the blood. The phthalein output seems to be a little reduced, namely about 50 per cent in two hours. The urea clearance test is rather low but it was not altogether owing to the large amount of fat in the blood. This much is quite clear and were that all, the situation would not be in any way puzzling. However, I cannot give a clear explanation for the enlargement of the liver and spleen. It is of course desirable to explain all of these abnormal findings on a single basis, therefore the first suggestion is that Mr. J. may have amyloid disease. This is a



possibility that I think cannot be definitely excluded and yet in my opinion the evidence is against it. It is impossible to do the Congo red test on account of the difficulty in reading the dye concentrations with so much fat in the serum. I am told we might have removed the fat from the serum and in that way made a satisfactory reading. Whether or not that is technically possible I cannot say. At any rate, the Congo red test is by no means a conclusive one but only suggestive. There has been much speculation about every possibility. One suggestion was that he might have universal xanthomatosis with involvement of the internal organs and not of the bones. This, I think, is a rather fantastic suggestion. I never have heard of such a condition and it seems to me altogether unlikely. This really is as far as I can go. I had a number of the men on the staff see Mr. J. to get their reaction and no one was able to add any suggestion of importance; only speculation with little fact to support it. I see nothing to do but proceed with the treatment of the nephritis and to ignore the other findings. There must be some degenerative disease of the liver and spleen but what it is I am unable to say."

A few days after he returned home he became very much more edematous. It was necessary at this time to use ammonium chloride and salyrgan-theophylline intravenously in 1 to 2 c.c. doses in order to get the edema cleared up. He was kept on Lextron as it had always been beneficial and was given multiple vitamins. As time went on he became thinner, weaker and was unable to retain food. He returned to the hospital on April 7, 1943. Examination revealed some ascites, the liver was a hand's breadth below the costal margin and the edge was sharp and smooth. The spleen was easily palpable. The lungs contained a few basal râles and the heart sounds were rapid and distant. There was no elevation of temperature. The laboratory findings were interesting: Hemoglobin 65 per cent, red blood cells 3,320,000, white blood cells, 9,000, polymorphonuclears 73 per cent, lymphocytes 27 per cent. The prothrombin time was 13 sec., and blood urea 179.88 mg. per cent. Urine was acid, 2 plus albumin, negative sugar, occasional granular cast, occasional pus cell and epithelial cell. There was no jaundice, but 500 c.c. of 15 per cent glucose were given intravenously daily for the nausea and to improve liver function. The course was rapidly downward. The heart sounds became weaker and more rapid, blood pressure remained about systolic 110 and diastolic 62. The temperature remained normal until the last three days when it went to 99.1 degrees. Pulmonary edema developed and he died on April 17, 1943. Although a definite diagnosis besides a nephrosis was not made, primary amyloidosis was still thought to be the most likely thing.

Autopsy was performed by Dr. H. H. Plowden with the following findings: "The body was that of a well developed and moderately nourished white man approximately 55 years of age, with prominent distention of the abdomen, and with considerable subcutaneous edema of the lower extremities. There was a marked general pallor of the tissues. At the request of the family, only the organs of the abdominal cavity were examined. In this cavity were 2,000 c.c. of straw-colored fluid, which escaped when the cavity was opened. The liver was approximately one and three quarters times its normal size, and extended downward two and one-half inches below the costal margin. This organ had a perfectly smooth glistening surface and rounded smooth margins and edges. Its color was a peculiar hard-to-describe pale pinkish waxy to glassy one. On gross section, the tissue of the organ cut with ease, and its internal color was the same as that of the surface. The tissue was intensely friable and gave the definite impression that it was infiltrated by some pathological process. Ordinary gross liver architecture could not be seen, aside from the larger divisions of the portal veins. The spleen was about five times the normal size, and was of the same color and texture and friability as already described for the liver. When gross sections of the spleen were removed and laid side by side with sections of the liver, they were no longer definitely distinguishable. They actually looked, felt and cut like sections of tissue from the same organ. The kidneys were of a

light pink color, glistening to waxy in appearance, and had a rough, very coarsely granular outer cortical surface. The capsules stripped easily, and the usual gross landmarks of the organ were obscured by some type of pathologic infiltrate similar to, but lighter in color than that already described in the liver and spleen. The gastrointestinal tract, the adrenal glands, the prostate, the urinary bladder, and the gall-bladder, were all approximately normal in appearance. Diagnosis: Amyloidosis of liver, spleen and kidneys. Tissue was removed for microscopic study from the liver, the spleen and the kidneys. Study of these sections shows substantially the same picture inasmuch as there was present in all sections varying amounts of the peculiar protein-like material known as amyloid. In the liver practically the entire normal structure of the organ had been destroyed, and the only liver cells remaining were occasional irregular, rather long cords of liver cells, made up of single liver cells placed end to end. In between these occasional cords of liver cells were very heavy masses of amyloid, which are pale pink staining, perfectly smooth and homogeneous, without any granularity whatsoever, thus giving a peculiar glassy appearance to most of the sections. Microscopic sections from the spleen showed substantially the same picture, except that, if possible, more amyloid was present in any given area than in the liver. There was practically no remaining splenic pulp. An occasional single splenic pulp cell could be found, and other than these, there remained only the blood vessels and previously formed supporting fibrous connective tissue framework. In the kidneys the amyloid material was not nearly so plentiful as in the two organs previously described. Here it was present only in the glomeruli and their capsules, which were almost entirely destroyed by its infiltrating and compressing qualities. Diagnosis: Amyloidosis of liver, spleen and kidneys."

#### COMMENT

The reported case is of particular interest for two reasons:

1. Because only a few cases of primary systemic amyloidosis showed such marked involvement of the liver, spleen and kidneys though these are commonly involved in the secondary type.

2. Because death was due to heart failure and azotemia. Of the 44 cases reported in only five was death attributed to the heart, very few had the nephrotic syndrome and only one had a true azotemia.

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## PALINDROMIC RHEUMATISM \*

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SINCE the publication of the description of palindromic rheumatism as a "new," oft recurring disease of joints apparently producing no articular residues" by Hench and Rosenberg,<sup>1, 2</sup> several additional case reports have appeared in the literature.<sup>3, 4, 5, 6, 7, 8</sup> However, because of the apparently infrequent occurrence of this condition, it is believed appropriate that we record our observations of a patient in whom the diagnosis of palindromic rheumatism seems well established in accordance with the description presented by Hench and Rosenberg.

Briefly, palindromic rheumatism is characterized by recurrent attacks of pain, swelling, redness, and disability generally of only one, but occasionally of more than one, small or large joint. The symptoms and findings generally last only a few hours or days and disappear rather rapidly to recur repeatedly at irregularly spaced intervals with no demonstrable residual joint changes. Constitutional reactions in the form of fever accompanying the attacks are unusual, but may definitely occur.<sup>9</sup> Laboratory tests including roentgenographic examinations of affected joints after numerous attacks reveal no persistently significant abnormal findings. The history, symptoms and findings of palindromic rheumatism are usually definite enough to permit a differentiation from other articular diseases such as rheumatoid arthritis, periarticular fibrositis, intermittent hydrarthrosis and rheumatic fever. A more difficult differentiation is that between the conditions described as "angioneural arthrosis" by Solis-Cohen<sup>10, 11</sup> or "allergic rheumatism" of Kahlmeter<sup>12</sup> and palindromic rheumatism. For a discussion of the similarities and differences the reader is referred to the discussion by Hench and Rosenberg.<sup>2</sup>

The etiology of palindromic rheumatism is still in doubt. Allergy, infection, and psychogenic factors have been suggested without any substantiation. Some patients believe that physical activity precipitates attacks. Our patient was of this opinion, hence was permitted to push a lawn mower. After two days of such activity he did develop pain, redness, and swelling of the metatarsophalangeal joint of the left great toe. However, attempts to precipitate other attacks by equally vigorous physical activity proved unsuccessful.

Inasmuch as definite etiological factors are not known Hench and Rosenberg<sup>2</sup> proposed the present designation for the disease as being a satisfactory descriptive term. They believed the term "rheumatism" preferable to "arthritis" in that it is more inclusive thereby being more applicable to not only the arthritis which occurs, but also to the peri-arthritis, para-arthritis, and the occasional subcutaneous nodules which may be features of the disease. The word, palindromic, was derived from the Greek and means literally "to run back" or "recurring" or "returning."

No uniformly effective therapy has been found for this condition. Removal of foci of infection and use of vaccines, bee venom, epinephrine, ephedrine, amphetamin, ergotamine tartrate, histaminase, histamine desensitization and diets low in purines or free of suspected food antigens have not been effective. Some patients feel that relief from nervous fatigue brings about improvement.

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In the series reported by Hench and Rosenberg, 15 per cent of the patients became well, 44 per cent improved somewhat, 26 per cent remained the same, 11 per cent became somewhat worse and one patient died of an unrelated illness. Apparently the only definite prognostic information one can give in any given case is the fact that no residual joint changes will result, for in spite of thousands of attacks in the series of patients reported by Hench and Rosenberg, not a single joint has demonstrated permanent changes.

#### CASE REPORT

A 31 year old enlisted man entered the hospital because of swelling of the joints of his right thumb for six hours. This swelling had come on rather suddenly and was associated with redness, pain and slight limitation of motion of the affected joints. The patient stated that he had had many similar attacks during the past 13 years.

The first attack of pain and swelling was noted in 1932 when the patient, while working on a farm, developed pain, redness and swelling of the right first metatarsophalangeal joint. He thought the swelling was due to walking on rough ground while plowing and did not seek any medical attention. The swelling subsided in about two days, leaving no pain or deformity. Approximately three weeks later he developed a similar swelling of the left index finger which subsided just as promptly without medication.

Since May, 1932, the patient had had frequent attacks of pain, redness and swelling about various joints of the body. These attacks came on in a few hours or a day and left just as promptly, usually lasting two to three days. He estimated that during the past 13 years, he had had over 300 such attacks. Usually only one or two joints were involved during an attack; however, he remembered one attack during which all the joints of the fingers of the left hand were involved at one time. The symptoms were never severe enough to incapacitate the patient, although they interfered with his efficiency in getting about in the performance of his work.

The patient's past history revealed that he had had malaria in 1934 and gonorrhea in 1936 with no apparent sequelae. He denied any history of hay fever, asthma, or other allergic disease. There was no history of articular disease in the patient's family; no familial history of allergy or tuberculosis was elicited. The patient's father was 60 years of age and was well. His mother died at the age of 57 because of "stomach trouble." The wife, two brothers and three sisters of the patient were in good health.

The patient was reared on a farm in East Texas and at the time of his coming into the Military Service was employed as a worker in the oil fields doing strenuous physical work. He had been in the Army for five years and had been assigned to the Air Corps within the Continental United States during his service.

Physical examination of the patient on admission revealed a well-developed, well-nourished, white male who did not appear acutely uncomfortable. The temperature was 98.4° F.; the pulse and respiratory rates were within normal limits. The blood pressure was 108 mm. Hg systolic and 68 diastolic. The tonsils were atrophic, the teeth revealed no abnormalities. There was no evidence of sinus disease. The hearing was diminished to 6/15, bilaterally, by the whispered voice test. Examination of the ears revealed no abnormalities; no topi were noted.

Moderate edema and redness of metacarpophalangeal and interphalangeal joints and the surrounding soft tissues of the right thumb were noted (see figure 1). There was slight limitation of motion of these joints as a result of the swelling. These findings remained for approximately 36 hours, then subsided gradually leaving no sequelae.



FIG. 1. Two views of the hands during an attack. Note the swelling of the right thumb, particularly about the interphalangeal joint

One of us has observed this patient during two other attacks. On one of these occasions the left first metatarsophalangeal joint was red, swollen and painful for approximately 24 hours, and during another attack, the distal interphalangeal joint of the left index finger was similarly involved for approximately 48 hours. The temperature, pulse and respirations were normal during these attacks, and the patient complained of no constitutional reactions.

The laboratory reports revealed no abnormalities of definite significance. The red blood count during the attack was 4,976,000; the hemoglobin was 85 per cent. The white blood count was 7,500, the differential count showing 52 per cent neutrophils, 28 per cent lymphocytes, 4 per cent monocytes, 1 per cent basophiles, 15 per cent eosinophiles. On five other differential counts between attacks, the eosinophiles ranged from 6 to 8 per cent. No explanation for this elevation can be given. Extensive allergic studies were not possible, and there was no clinical evidence of any parasitic infestation. The urine examination was normal. The sedimentation rate during attacks was elevated to as high as 21 mm. per hour (Cutler method), but between attacks was always found to be normal. The Kahn test was negative. Examination of the prostatic fluid showed one to four pus cells per high power field. The blood uric acid was 2.8 mg. per hundred cubic centimeters; the urea-nitrogen 15 mg. per hundred cubic centimeters, the chlorides 445 mg. per cent, and the blood cholesterol 169 mg. per hundred cubic centimeters. The agglutination test for undulant fever was negative. The electrocardiogram was normal. A roentgenogram of the chest revealed no abnormalities and roentgenograms of the hands, wrists, elbows, feet, ankles and knee joints showed no evidence of pathologic changes.

Inasmuch as the attacks in this patient were not incapacitating, the patient was returned to duty with advice concerning avoidance of strenuous physical activity, since he believed such activity was a factor in the production of his symptoms, although we could not prove this as an etiologic factor.

#### COMMENT

This patient presents the symptoms and findings of recurrent attacks of acute swelling, redness, pain, and tenderness of various joints and their surrounding tissues which have been described by Hench and Rosenberg as characterizing palindromic rheumatism. The irregularity of the intervals between attacks, the rapid onset and subsidence of the attacks, and the complete lack of demonstrable sequelae are also characteristic of the condition. The significance of an increase in the eosinophile count in this patient is in doubt. Three patients in the series reported by Hench and Rosenberg had slight elevations of the percentages of eosinophiles between attacks, but no increases were noted during attacks.

Although the etiology of this condition and its treatment are unknown, it is believed important that it be recognized, since patients with palindromic rheumatism may be reassured that, in spite of the frequency and severity of their attacks, no joint deformities will result in contrast to the deformities often resulting from other types of articular disease.

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## EDITORIAL

### *PSEUDOHEMOPHILIA*

HEMORRHAGIC diseases present a complicated problem, and there is still much uncertainty regarding the fundamental nature and relationship of many of the cases showing such disorders. This may be attributed in part to the number and complexity of the factors involved in hemostasis and to their variability, as well as to the inadequacy, cumbersome nature and relative lack of precision of many of the laboratory procedures available for their investigation. Variations in technic in the hands of different workers have also been confusing.

It has been customary to classify cases of hemorrhagic disease into three main groups according to their pathogenesis: those with a deficiency of blood platelets, those with some disturbance of the coagulation factors of the blood, and those with a demonstrable or presumed abnormality of the walls of the minute vessels.

The first group includes the primary and secondary thrombocytopenic purpuras. This group is relatively clear cut, and most of the cases can be recognized easily by the characteristic reduction in blood platelets, prolonged bleeding time, defective clot retraction and positive tourniquet test, whereas the coagulation time is usually normal.

The second group includes hemophilia and those cases of bleeding associated with a reduction of prothrombin or of fibrinogen. These conditions also can usually be distinguished clearly by the available tests. Hemophilia is nearly the antithesis of thrombocytopenic purpura, with its prolonged coagulation time, but normal platelet count, bleeding time, negative tourniquet test and (eventually) normal clot retractility, as well as its peculiar hereditary nature.

The third group includes cases which have been termed nonthrombocytopenic purpura or anaphylactoid purpura, including the syndromes described by Schoenlein and by Henoch. Here too would be included cases of hereditary hemorrhagic telangiectasia, in which all other factors are normal and localized abnormalities in the capillaries are conspicuous and easily demonstrable. In general these cases are less well understood because of the lack of adequate methods of testing the functional integrity of the vessels.

Although most cases of hemorrhagic disease can now be fitted into well recognized groups, there have been a considerable number of "atypical" cases reported during the past 30 years. The recognition and separation of the hypoprothrombinemias is a relatively recent accomplishment. Many reports have appeared describing other groups of cases which it was thought might constitute a distinct syndrome.

One of the earliest and still frequently quoted contributions was that of



Glanzmann.<sup>1</sup> He reported eight families containing from two to many bleeders in several generations, in which the tendency affected and was transmitted by both sexes. The cases were characterized clinically by bleeding from the mucous membranes, from cuts and abrasions, operative wounds and after dental extractions, but without purpura and with little tendency to intracutaneous bleeding. They were characterized by a normal coagulation time, a normal (or insignificantly reduced) platelet count, and a normal bleeding time,<sup>2</sup> but clot retraction was defective or absent. He described morphological and functional abnormalities in the platelets which he thought were responsible for the disturbance, and termed the condition "thrombasthenia." Except for two partially confirmatory reports<sup>3,4</sup> which appeared shortly after Glanzmann's article, not a single case conforming to his description has since been recorded. One must conclude either that this syndrome is excessively rare, or that Glanzmann's observations were faulty. His conception of "thrombasthenia," however, a functional deficiency of the platelets, has persisted and is still a matter of controversy.

von Willebrand (in 1926 and more fully in 1929<sup>5</sup>) reported a large series of cases which resembled those of Glanzmann as far as their clinical features and familial occurrence are concerned. They occurred in three families of Swedish descent which had lived for a thousand years in isolated communities in Finland where there was considerable inbreeding and but little admixture with outside populations. He obtained records of 124 members of these families, of whom 48 gave a history of bleeding; 17 were males and 31 females, of whom 10 females died of hemorrhage. He was able to study 18 cases, of which 13 on some occasion showed the following characteristic features: a normal coagulation time, a normal or high platelet count, and normal clot retractility, but a prolonged bleeding time and in the severer cases a positive tourniquet test. The bleeding time, however, was not uniformly or invariably prolonged; it sometimes varied on different occasions in the same patient and tended approximately to parallel the severity of the symptoms.

von Willebrand attributed the bleeding principally to a functional abnormality of the platelets ("Thrombopathie"), but recognized a "vascular component." He advanced evidence—not entirely convincing—that the platelets agglutinated less readily in a capillary glass tube than did those of normal blood.

<sup>1</sup> GLANZMANN, E.: Hereditäre hämorrhagische Thrombasthenie. Ein Beitrag zur Pathologie der Blutplättchen, *Jahrb. d. Kinderh.*, 1918, lxxxviii, 1-42, 113-141.

<sup>2</sup> Glanzmann's article has been misquoted in many journal articles and textbooks in stating that the bleeding time was prolonged. If a few cases of typical thrombocytopenic purpura, so diagnosed by Glanzmann, are disregarded, the bleeding time in all his cases is recorded as *normal*.

<sup>3</sup> KRÖMECKE, F.: Zur Frage der hereditären hämorrhagischen Diathese (Thrombasthenie), *Deutsch. med. Wchnschr.*, 1922, xlviii, 1102-1105.

<sup>4</sup> ZANDE, F. VAN DER: Pseudohemophilia, *Nederl. tijdschr. v. geneesk.*, 1923, lxxvii, 544-553.

<sup>5</sup> V. WILLEBRAND, E. A., and JÜRGENS, R.: Über ein neues vererbbares Blutungsübel: Die konstitutionelle Thrombopathie, *Deutsch. Arch. klin. Med.*, 1933, clxxv, 453-583.

Because of the much greater incidence and severity of the disease in females in his series, he thought the defect was inherited as a sex-linked dominant character. The transmission from father to son, brought out more strikingly in subsequent studies by other observers, indicates that this can not be the case, and the trait is probably inherited as a simple incomplete dominant character of ordinary type. A number of cases clinically indistinguishable have since been reported<sup>6</sup> without any familial history of bleeding, and the disease can not be excluded on this ground. The same is true of hemophilia.

von Willebrand's observations in the main have been confirmed by many subsequent observers. Among others, Minot<sup>7</sup> studied five cases in a family of 31, of whom 11 (over four generations of males) were bleeders. Clinically and hematologically they corresponded closely to von Willebrand's description. Little and Ayres<sup>8</sup> studied two sisters in a family of 71, of which 24 gave a history of bleeding. These two cases differed only in having splenic enlargement. One bled to death following attempted splenectomy.

Geiger and Evans<sup>9</sup> reported a similar case of severe gastrointestinal bleeding in a man and in two of his children in a family of nine, of whom five were bleeders. They present an excellent review of previously reported cases. Macfarlane<sup>10</sup> studied five such cases, and Estren, Médal and Dameshek<sup>6</sup> reported 11 cases which were typical except that in only five was a family history of bleeding obtained.

The hematological features of these cases have already been described. Cytologically they have been normal or showed those changes which are commonly associated with hemorrhage. Clinically they present a fairly characteristic picture which differs in some respects from both hemophilia and thrombocytopenic purpura.

Bleeding commonly starts in early life, sometimes in infancy, and is often troublesome in small children whose tumbles and minor traumata frequently result in extensive ecchymoses and persistent oozing from superficial abrasions. It may persist throughout life, but in many cases has become less troublesome after adolescence, particularly the tendency to epistaxis.

Bleeding from the mucous membranes, persistent and often profuse, is a common and highly characteristic feature. Epistaxis is very common, as well as bleeding from the gums and from the uterus. Bleeding occurs

<sup>6</sup> ESTREN, S., MÉDAL, L. S., and DAMESHEK, W.: Pseudohemophilia, *Blood*, 1946, i, 504-533.

<sup>7</sup> MINOT, G. R.: A familial hemorrhagic condition associated with prolongation of the bleeding time, *Am. Jr. Med. Sci.*, 1928, clxxv, 301-306.

<sup>8</sup> LITTLE, W. D., and AYRES, W. W.: Hemorrhagic disease: familial bleeding tendency of unusual type with splenomegaly, affecting and transmitted by both males and females, *Jr. Am. Med. Assoc.*, 1928, xci, 1251-1252.

<sup>9</sup> GEIGER, A., and EVANS, E. G.: Atypical hereditary hemorrhagic syndromes, *Internat. Clin.*, 1938, ii, 135-157.

<sup>10</sup> MACFARLANE, R. G.: Critical review: The mechanism of hemostasis, *Quart. Jr. Med.*, 1941, x, 1-29.

less frequently from the gastrointestinal tract and only occasionally from the kidneys or lungs. Persistent oozing from superficial cuts and abrasions is common and resembles that in hemophilia. Bleeding often occurs from operative incisions, is extremely troublesome and may be fatal. These patients are poor "surgical risks," and unessential operations and particularly splenectomy should be avoided. They may be even worse risks than cases of hemophilia or thrombocytopenic purpura, since transfusions (or injections of antihemophilic globulin in hemophilia) will usually stop bleeding temporarily, whereas in this disease they have relatively little or no effect upon the bleeding. Troublesome bleeding is common after dental extractions and may occur in children after loss of deciduous teeth.

Bleeding into the skin is common in the form of ecchymoses, usually following trauma, but is less conspicuous than in thrombocytopenic purpura, and typical petechiae are much less common. Bleeding into the joints has occurred in several cases, but is relatively uncommon, in contrast to hemophilia. Intracranial and retinal hemorrhages have been recorded, but are very rare.

The tendency to bleed varies markedly in different individuals and in the same individual at different times. The tendency does not necessarily parallel the length of the bleeding time or the result of the tourniquet test, although there is a general tendency to do so. Precise figures as to mortality are not available. As in hemophilia, there is a high probability of recovery from any one individual attack of bleeding, but the "accumulated" mortality is substantial. Of the 62 collected cases reported by Estren et al.<sup>6</sup> which had been adequately studied, only two died of hemorrhage. This is undoubtedly an underestimate of the ultimate mortality. Geiger and Evans<sup>9</sup> reported 17 fatalities among 97 bleeders, collected largely from previous reports. As adequate blood studies had been made in only one of these fatal cases, it is possible that in some the bleeding may have been due to some other cause. However, as other bleeders in the same families showed typical manifestations of the disease, there is a strong presumption that most of them died as a result of it. Geiger and Evans' figures may underestimate the ultimate mortality, as many of the survivors were not followed throughout their life span. All but one of the fatal cases were in women. This greater mortality is not due primarily to the additional risk from uterine bleeding, as there was a greater general tendency to bleed in most of these cases. The reason for this sex difference is not known.

The pathogenesis of the bleeding is still undetermined. Attempts to demonstrate a functional defect of the platelets have been mentioned, but the evidence is not convincing. It is probably not due to a dysfunction of the spleen. In most cases the organ has not been enlarged, or at least not palpable. In the few cases in which splenectomy has been carried out, there has been little if any effect on the bleeding. At best, it is in no way comparable with that often seen following splenectomy in thrombocytopenic purpura.

Macfarlane<sup>10</sup> has emphasized the importance of the rôle played by the minute vessels in hemostasis. Normally trauma to these vessels is quickly followed by a constriction which mechanically checks oozing until sufficient time has elapsed to permit agglutination of platelets and the formation of a firm clot which will occlude them. In certain pathologic states including this syndrome and thrombocytopenic purpura, these vessels appear to be abnormal, they fail to undergo constriction after injury, and permit continuous oozing which prevents the formation of an occluding clot or thrombus. He reports that the capillary loops in the nail beds in these diseases are distended and tortuous. When a single capillary loop in a normal individual is punctured with a fine glass fiber, after a slight hemorrhage it quickly contracts and disappears and remains invisible for from 20 minutes to two hours. In these diseases there was no constriction after puncture, and bleeding into the tissues persisted.

These observations of abnormal-appearing capillary loops which fail to constrict and which bleed progressively after injury have been confirmed. Perkins<sup>11</sup> has reported similar findings in one case, and Levy<sup>12</sup> in three cases of this syndrome. It seems possible, therefore, that vascular abnormalities play an important and perhaps a major rôle in the bleeding tendency, although the tourniquet test is not so uniformly and strongly positive as might be expected if this is the case. The existence of some associated defect of coagulation, possibly due to an abnormality of the platelets, has not been excluded.

Treatment has been unsatisfactory. Superficial bleeding can usually be controlled by local applications of fibrin foam and thrombin solution under moderate pressure. Internal hemorrhages, however, have been relatively uninfluenced by transfusions and other customary procedures, although they counteract the effects of acute blood loss. There are spontaneous variations in the tendency to bleed, however, and in a majority of the cases bleeding eventually ceases before exsanguination occurs.

In addition to those cases precisely conforming to this description, many others have been reported which differ in one or more of their hematological features. As Geiger and Evans<sup>9</sup> have pointed out, some of these more closely resemble hemophilia, others thrombocytopenic purpura, and they might be regarded as transitional stages between these two extremes. They have questioned the possibility of subdividing these cases into clear cut groups on such a basis, pointing out that notable differences may be found between two bleeders in the same family and even in the same individual on different occasions. In the past vascular abnormalities have received inadequate attention, and until these can be more accurately appraised, it is unlikely that any satisfactory classification can be worked out.

<sup>11</sup> PERKINS, W.: Pseudohemophilia: Case study, *Blood*, 1946, i, 497-503.

<sup>12</sup> LEVY, L. II: Non-hemophilic hereditary hemorrhagic diathesis: Report of a family of bleeders, *Ann. Int. Med.*, in press.

The terminology of these syndromes is chaotic. Several different names, all unsatisfactory, have been applied to this group. Thrombasthenia implies an etiology which is not proved and not generally accepted. Pseudohemophilia is perhaps equally unsatisfactory, and it has also been applied to other unrelated hemorrhagic tendencies. It has been used more often than any other in the recent literature, however, and if qualified by some such term as "von Willebrand type," it should not be misleading.

Pseudohemophilia is of academic interest because primary vascular abnormalities appear to be more significant or at least more evident than in most of the other hemorrhagic diseases. It is also of practical significance. It is evidently more common than has been appreciated, probably at least as common as hemophilia, and it is not necessarily familial or at least demonstrably so. Recognition of the tendency is particularly important in order to avoid unexpected and unnecessary risks involved in unessential operations. Cronkite and Lozner<sup>13</sup> have reported such a case, an otherwise healthy soldier who bled repeatedly and protractedly after a simple hemorrhoidectomy. The occurrence of previous hemorrhage in the patient and of other bleeders in the family was not discovered until after the postoperative hemorrhages began.

P. W. C.

<sup>13</sup> CRONKITE, E. P., and LOZNER, E. L.: Hereditary hemorrhagic thrombasthenia with severe posthemorrhoidectomy hemorrhage, U. S. Naval Med. Bull., 1944, xlii, 161-164.

## REVIEWS

*Pharmacology and Therapeutics*. Thirteenth Edition. Originally Written by ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S. Revised by ARTHUR GROLLMAN, A.B., Ph.D., M.D., F.A.C.P., and DONALD SLAUGHTER, B.S., M.D. 868 pages; 24 × 16 cm. Lea and Febiger, Philadelphia. 1947. Price, \$8.50.

This, the 13th edition of this classic pharmacology text, has been reëdited and revised by two eminently qualified authorities. The junior author has revised the section on central nervous system depressants. The remainder of the book shows the skillful hand of Dr. Grollman.

To most practitioners of medicine, Cushny's *Pharmacology* needs no introduction for it has long been a standard text in this field. In bringing the book up to date, the present revisers have incorporated changes introduced by the publication of the 12th revision of the U. S. Pharmacopoeia and the British Pharmacopoeia of 1932.

The introduction deals with the method of action of drugs, their chemical character, the pharmacopoeias and pharmacopoeial preparations, and biological assays. As in previous editions, the book is divided into six major parts: Part I, The Action of Inorganic Substances; Part II, Substances Which Are Characterized Chiefly by Their Local Action; Part III, Substances Characterized Chiefly by Their Action After Absorption; Part IV, Anthelmintics; Part V, Antiseptics and Disinfectants; Part VI, Vaccines and Biologicals.

The section on general anesthetics appears to be very brief and, like most current textbooks in pharmacology, provides a very elaborate discussion of the pharmacology of chloroform, while the newer general anesthetics are given but passing mention.

The volume, however, in most respects is abreast of recent developments in the field of pharmacology. For example, one finds a discussion of folic acid, para-aminobenzoic acid and vitamin K adequately presented under the section on vitamins or accessory food substances. Also, such recent discoveries as the production of experimental diabetes by the injection of alloxan are included, and in the section on analgesics, isonipECAINE is discussed.

As a whole, this edition of Cushny's original work appears to be well presented and will recommend itself to the medical student, the practitioner of medicine and the teacher in the field of pharmacology.

C. J. C.

*Hygiene*. Fourth Edition. By FLORENCE L. MEREDITH, B.Sc., M.D. 837 pages; 24 × 16.5 cm. 1946. The Blakiston Company, Philadelphia. Price, \$4.00.

This clearly and simply written textbook is probably well suited to the needs of a college course designed to introduce the student to the problem of health and hygiene. It is divided into nine sections, including parts devoted to anatomy and physiology, history of medicine, infection, hygiene of everyday life, and, finally, a very sound section on mental health.

The work is too elementary to be used by medical students, but should help the undergraduate to understand some of the problems of medical care. The practitioner may find it useful to orient patients in relation to his own work.

T. N. C.

## BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Gastroenterology in General Practice.* By LOUIS PELNER, M.D. 283 pages; 26 × 17.5 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, \$7.50.

*Textbook of Medical Treatment.* Fourth Edition. By Various Authors. Edited by D. M. DUNLOP, M.D., F.R.C.P., L. S. DAVIDSON, M.D., F.R.C.P., and J. W. McNEE, M.D., F.R.C.P. 923 pages; 25 × 17.5 cm. 1946. The Williams & Wilkins Company, Baltimore. Price, \$8.00.

*Clinical Hematology.* Second Edition. By MAXWELL M. WINTROBE, M.D., Ph.D. 862 pages; 24 × 15.5 cm. 1946. Lea & Febiger, Philadelphia, Pa. Price, \$11.00.

*The Nature of Disease Up To Date.* An Outline of a Unitary Theory. By J. E. R. McDONAGH, F.R.C.S. Edited by MARK CLEMENT. 168 pages; 22 × 14.5 cm. 1946. William Heinemann, London. (To be obtained from Grune & Stratton, New York.) Price, 15 s.

*Heparin in the Treatment of Thrombosis.* Second Edition. By J. ERIK JORPES, M.D. Foreword by J. R. LEARMONTH, C.B.E., Ch.M., F.R.C.S.E. 260 pages; 22.5 × 14 cm. 1947. Oxford University Press, New York. Price, \$6.50.

*Parenteral Alimentation in Surgery.* By ROBERT ELMAN, M.D., Assoc. Prof. Clin. Surg., Washington University School of Medicine. 284 pages; 24 × 15.5 cm. 1947. Paul B. Hoeber, Inc., New York. Price, \$4.50.

*Pharmacology and Therapeutics.* Thirteenth Edition, Thoroughly Revised. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S. Revised by ARTHUR GROLLMAN, M.D., F.A.C.P., and DONALD SLAUGHTER, B.S., M.D. 868 pages; 24 × 16 cm. 1947. Lea & Febiger, Philadelphia. Price, \$8.50.

*Cardiovascular Diseases.* By DAVID SCHERF, M.D., F.A.C.P., and LINN J. BOYD, M.D., F.A.C.P., Prof. Medicine, New York Medical College. 478 pages; 26 × 18.5 cm. J. B. Lippincott Company, Philadelphia. Price, \$10.00.

*Foreseeing and Forestalling Tuberculosis.* A Symposium. By W. E. OGDEN, M.D., F.A.C.P., F.C.C.P., G. C. ANGLIN, M.B., F.A.C.P., F.C.C.P., and W. C. KRUGER, M.B., et al., Toronto, Canada. 55 pages. Reprinted from "Diseases of the Chest."

## COLLEGE NEWS NOTES

### NOMINATIONS FOR A.C.P. ELECTIVE OFFICES, 1947-48

In accordance with the By-laws of The American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1947-48, are herewith announced and published:

*President Elect*.....Walter W. Palmer, New York, N. Y.  
*First Vice President*.....Reginald Fitz, Boston, Mass.  
*Second Vice President*.....Francis G. Blake, New Haven, Conn.  
*Third Vice President*.....Charles T. Stone, Galveston, Tex.

Regular elections will take place at the 1947 Annual Session at Chicago, April 28-May 2. The Business Meeting will be held Thursday afternoon, May 1, in the Grand Ballroom of the Palmer House.

The election of nominees shall be by the Fellows and Masters of the College. The above Nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations for members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-laws.

Respectfully submitted,

Ralph A. Kinsella, St. Louis, Mo.  
Asa L. Lincoln, New York, N. Y.  
Jonathan C. Meakins, Montreal, Can.  
George F. Strong, Vancouver, Can.  
James J. Waring, *Chairman*, Denver, Colo.

*Committee on Nominations*

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### ADDITIONAL LIFE MEMBERS

Grateful acknowledgment is made of subscriptions to Life Memberships, received January 20 through February 17, 1947, from the following Fellows of the College:

Clarence L. Andrews, Atlantic City, N. J.  
Theodore F. Bach, Philadelphia, Pa.  
John V. Barrow, Los Angeles, Calif.  
Paul J. Breslich, Minot, N. D.  
Madelaine R. Brown, Boston, Mass.  
Roland Cummings, Los Angeles, Calif.  
Maurice A. Donovan, Schenectady, N. Y.  
Thomas B. Dunn, Oakland, Calif.  
Harry E. Flansburg, Lincoln, Nebr.  
William W. Fox, Atlantic City, N. J.  
Cleo R. Gatley, Pontiac, Mich.  
James T. Gilbert, Jr., Bowling Green, Ky.  
Carl A. Hartung, Chattanooga, Tenn.  
Frederick K. Herpel, W. Palm Beach, Fla.  
Edwin F. Hirsch, Chicago, Ill.  
B. Smith Hopkins, Jr., Urbana, Ill.



Albert A. Hornor, Boston, Mass.  
James E. Hunter, Seattle, Wash.  
Wingate M. Johnson, Winston-Salem, N. C.  
Gordon R. Kamman, St. Paul, Minn.  
Joseph Kaufmann, Montreal, Can.  
Donald L. Kegaries, Rapid City, S. D.  
Clyde H. Kelchner, Allentown, Pa.  
O. B. Kiel, Wichita Falls, Tex.  
Harold I. Kinsey, Toronto, Can.  
Elmer A. Kleefield, Forest Hills, N. Y.  
Roy L. Leadingham, Atlanta, Ga.  
Charles E. Leonard, Oklahoma City, Okla.  
Robert C. Levy, Chicago, Ill.  
Horace R. Livengood, Elizabeth, N. J.  
William C. Menninger, Topeka, Kans.  
F. D. Mohle, Houston, Tex.  
P. Morales-Otero, Santurce, P. R.  
Samuel A. Munford, Clifton Springs, N. Y.  
Clarence W. Olsen, Beverly Hills, Calif.  
Hubert M. Parker, Kansas City, Mo.  
Joseph M. Perret, New Orleans, La.  
Frank B. Queen, Portland, Ore.  
Edward U. Reed, Los Angeles, Calif.  
Rufus S. Reeves, Philadelphia, Pa.  
Edward C. Reifenstein, Sr., Syracuse, N. Y.  
E. Clarence Rice, Washington, D. C.  
Carl O. Rinder, Chicago, Ill.  
H. Milton Rogers, St. Petersburg, Fla.  
Albert H. Rowe, Oakland, Calif.  
Cecil L. Rudesill, Indianapolis, Ind.  
Jacob Schwartz, Brooklyn, N. Y.  
Kenneth K. Sherwood, Kirkland, Wash.  
George T. Strodl, New York, N. Y.  
Amadeo Vicente-Mastellari, Panama, R. P.  
James C. Waddell, Beatrice, Nebr.  
Robert P. Wallace, New York, N. Y.  
Leslie R. Webb, Springfield, Mo.  
Joseph Weinstein, Brooklyn, N. Y.  
Otto G. Wiedman, Hartford, Conn.  
F. Eugene Zemp, Columbia, S. C.

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REGIONAL MEETING PLANNED FOR DELAWARE, MARYLAND AND THE  
DISTRICT OF COLUMBIA, BALTIMORE, APRIL 5, 1947

At the time of this writing, Governor Wetherbee Fort has prepared, with the coöperation of Drs. Lewis B. Flinn and Wallace M. Yater, College Governors for Delaware and District of Columbia, respectively, the tentative program of a regional meeting to take place April 5. The morning session will occur in the Gordon Wilson Hall of the University of Maryland Hospital, and will be followed by lunch in the Phipps Clinic and an afternoon session in the Hurd Lecture Hall of the Johns Hopkins Hospital.

The program will include the following papers: Studies in Rh Isoimmunization, Milton S. Sacks, F.A.C.P.; Some Observations on and Treatment of Peripheral Vascular Diseases, Louis Krause, F.A.C.P.; Use of Tracer Amounts of Radioactive Iodine for the Detection of Aberrant Thyroid Tissue, Edward F. Cotter (Associate); Some Aspects of the Surgical Treatment of Heart Disease, Alfred Blalock, F.A.C.S.; Modern Treatment of Cirrhosis of the Liver, W. Halsey Barker, F.A.C.P.; Experience with Thiouracil Treatment of Hyperthyroidism, Elliott V. Newman (by invitation); Use of the Thymol Turbidity Test in the Study of Liver Disease, Richard Mirick (by invitation); Periodic Vascular Head Pain, Edmund L. Keeney, F.A.C.P.; all of Baltimore, Md. Also: Extra Pulmonary Pneumococcal Infections, Albert A. Pearre, F.A.C.P., Frederick, Md.; County Medical Problems, Page C. Jett (by invitation), Prince Frederick, Md.; Value of Special Electrocardiographic Studies in General Hospitals, James S. Taylor (MC), USA, (Associate), Washington, D. C.; Paroxysmal Supraventricular Tachycardia with Functional Auricular-Ventricular Block, Joseph M. Barker (Associate), Washington, D. C.; Aphorisms Based on the Observation of 1037 Treated Cases of Peptic Ulcer, Lewis Gunther (MC), USN, (Associate), Bethesda, Md.; Preliminary Report on the Result of Smallpox Vaccination in 50,000 Industrial Workers, Lemuel C. McGee, F.A.C.P., Wilmington, Del.

In its work, the local committee on arrangements is receiving the valued cooperation of Dr. E. L. Crosby, Jr., Superintendent of the Johns Hopkins Hospital; of Dr. Abner McG. Harvey, Professor of Medicine in the Johns Hopkins University; and of Dr. Maurice C. Pincoffs, F.A.C.P., Professor of Medicine in the University of Maryland. The printed program will be distributed to all Fellows and Associates in this area.

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#### SPECIALTY BOARD EXAMINATIONS

American Board of Dermatology and Syphilology; George M. Lewis, M.D., Secretary-Treasurer, 66 E. 66th St., New York 21, N. Y. Applications closed February 17. Written examinations, March 24, 1947; oral examinations, April 25-27, New York, N. Y.

American Board of Internal Medicine; William A. Werrell, M.D., Assistant Secretary-Treasurer, 1-W. Main St., Madison 3, Wis. Written examinations, March 17, 1947; October 20, 1947 (closing date, June 1). Oral examinations, April 24-26, 1947, Chicago, Ill. (closing date, March 15); June 5-7, 1947, Philadelphia, Pa. (closing date, April 1).

American Board of Pathology; Robert A. Moore, M.D., Secretary, Euclid Ave. and Kingshighway, St. Louis 10, Mo. Examination, June 3-4, 1947, Philadelphia, Pa. (closing date, April 15).

American Board of Pediatrics; Lee F. Hill, M.D., Secretary-Treasurer, 1818 12th St., Des Moines, Iowa. Examinations, April 25-27, 1947, The Palmer House, Chicago, Ill.; May 10-11, 1947, The Children's Hospital, Buffalo, N. Y.

American Board of Psychiatry and Neurology; F. J. Braceland, M.D., Secretary-Treasurer, 102-10 2nd Ave., S.W., Rochester, Minn. Examinations (tentative dates), May 15-17, 1947, Philadelphia, Pa.

American Board of Radiology; B. R. Kirklin, M.D., Secretary-Treasurer, 102-10 2nd Ave., S.W., Rochester, Minn. Examinations, June 4-8, 1947, Atlantic City, N. J.

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The American Trudeau Society, cooperating with the University of Colorado Medical School, will offer a Postgraduate Course in Thoracic Diseases, July 28

to August 9, 1947, in Denver, Colo. Fee for the course will be \$100.00. Inquiries should be addressed to Cameron St. C. Guild, M.D., Executive Secretary of this Society, 1790 Broadway 19, N. Y.

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The 4th International Cancer Research Conference will be held September 2 to 7, 1947 in St. Louis, Mo. The 75th Annual Meeting of the American Public Health Association will take place October 6 to 10, 1947 at Atlantic City, N. J.

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The 11th Annual Postgraduate Institute of the Philadelphia County Medical Society will be held at the Bellevue-Stratford Hotel, April 15 to 18, 1947. The theme will be "Symposia on Medical Progress." Subjects discussed will include thyroid problems, diabetes, vitamins and hormones, intestinal disorders, kidney pathology, peripheral vascular diseases, antibiotics, hypertension, diseases of the lung, neuropsychiatry, stomach and duodenum, allergy, skin disorders, and otolaryngological diseases. Two evening meetings at the Society Building will concern childhood and infancy disorders, and obstetrical and gynecological problems. There will be technical and scientific exhibits.

The registration fee for non-members is \$5.00 for the course. Out-of-town physicians planning to attend are urged to make their hotel reservations immediately. Further information may be had from Gilson C. Engel, M.D., Director, 301 South 21st St., Philadelphia 3, Pa.

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The third annual convention of the American Society for the Study of Sterility will be held at the Hotel Strand, Atlantic City, New Jersey, on June 7 and 8, 1947, preceding the annual A.M.A. Convention. The general theme of the meetings will be that of attempting to disseminate to the physician treating marital infertility an overall picture of the latest advances in reproduction. The convention will include original papers, round table discussions, scientific exhibits, and personal demonstrations. Registration for the sessions is open to members of the medical and allied professions.

Additional information may be obtained from the secretary, Dr. John O. Haman, 490 Post Street, San Francisco, Calif.

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#### REPORTS ON RECENT REGIONAL MEETINGS

##### *I. New England—January 28, 1947*

Held at Hanover, N. H., this meeting was reported as a very successful one. The fine program was printed in the February News Notes. Attendance was as follows: Connecticut, 10; Massachusetts, 31; Maine, 9; New Hampshire, 57; New York, 1; Rhode Island, 8; Vermont, 12.

##### *II. Lansing, Michigan—January 29, 1947*

A Regional Meeting of the College was held at Lansing during the afternoon and evening of January 29th. A severe blizzard on that date interfered with the attendance; there were 35 members present, according to the report by Dr. William M. LeFevre, F.A.C.P., Muskegon, Secretary. Arrangements were made by Dr. Milton Shaw, F.A.C.P., Lansing; and Dr. Leo G. Christian, F.A.C.P., Lansing, acted as chairman of the meeting. The program consisted in the following papers: Non-

surgical Treatment of Lung Abscess, Christopher Stringer, F.A.C.P.; Simulation of Angina Pectoris by Diaphragmatic Hernia, Joseph Rozan (by invitation); Salmonellosis and Shigellosis, H. E. Cope (by invitation); Blood Derivatives, A. B. Mitchell (by invitation); Rh Factor, G. D. Cummings (by invitation).

### *III. Eastern Pennsylvania—February 7, 1947*

The Ninth Annual Regional Meeting of The College for Eastern Pennsylvania was held at Philadelphia on February 7. The States of Delaware and New Jersey were invited to join in and a good representation of the members was present. There were also in attendance those who were taking The College postgraduate course in Growth, Isotopes, and Tumor Formation. In fact, the morning program of the postgraduate course was open also for all those in attendance at the Regional Meeting.

Papers on the formal program were of uniformly excellent quality. A midday luncheon was held at The College Headquarters with a hundred and ninety-five in attendance and a dinner meeting was held at the Warwick Hotel with an attendance of two hundred and fifty. In all, more than 300 members from the area participated in some part of the Meeting. Chief speakers at the evening dinner meeting were Dr. Alexander M. Burgess, College Governor for Rhode Island and Member of the American Board of Internal Medicine, and Mr. E. R. Loveland, Executive Secretary of The College.

### *IV. Birmingham, Alabama—February 8, 1947*

The State of Alabama, under the Governorship of Dr. E. Dice Lineberry, held its first formal Regional Meeting for that state at Birmingham, February 8, 1947. There was a gratifyingly fine attendance with practically all the members of The College present from Alabama, some visitors from adjoining states and a considerable number of guests.

The afternoon program included the following papers: Primary Splenic Hematopenia, William H. Riser, Jr. (by invitation); Recent Studies on the Chemotherapy of Leukemia, Howard E. Skipper, Ph.D. (by invitation); Anticoagulants in Acute Myocardial Infarction, Oliver Welch (Associate); The University of Alabama Medical College, Roy D. Kracke, Dean (by invitation); Clinical-Pathological Conference, James S. McLester, F.A.C.P., and Roger D. Baker (by invitation).

Dr. Hugh J. Morgan, President-Elect of The College, Nashville, Tenn., was the chief speaker at the dinner.

Following the Meeting, an Executive Session was held and resolutions were adopted providing that Alabama shall hold a regular Annual Regional Meeting under the direction of its Governor. Dr. Olney Russell, F.A.C.P., was elected Secretary-Treasurer for future meetings of this character.

Total attendance exceeded one hundred.

### *V. Wichita, Kansas—March 21, 1947*

Annual meetings for members of the College residing in Kansas have been resumed. The program of this first post-war meeting, arranged by College Governor Harold H. Jones, Winfield, included a morning Clinical-Pathological Conference, conducted at the St. Francis Hospital by Christian A. Hellwig, M.D. (by invitation); luncheon at the Allis Hotel; and an afternoon session devoted to the following topics: Causes and Treatment of Edema, George F. Corrigan, F.A.C.P., Wichita; Cytochrome C, Samuel Zelman (by invitation), Topeka; Electrocardiogram in Angina Pectoris, Fred J. McEwen, F.A.C.P., Wichita; Medical Advances in Relation to Colloidal Chemistry, Clarence W. Erickson, F.A.C.P., Pittsburg; Hypoglycemia in

the Fatigue Syndrome, Lee H. Leger, F.A.C.P., Kansas City; Protein Metabolism, George A. Westfall, F.A.C.P., Halstead; Some Aspects of Choline Metabolism, Frederic W. Hall (Associate), Winfield.

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#### DR. PAULLIN AWARDED MEDAL FOR MERIT

Dr. James E. Paullin, Atlanta, Ga., Regent and former President of the College, received the President's Medal for Merit on January 31, 1947, at the hands of Secretary of the Navy Forrestal. The citation read as follows:

"Dr. James Edgar Paullin, for exceptionally meritorious conduct in the performance of outstanding services to the United States since 1943. Dr. Paullin served as Honorary Consultant to the Bureau of Medicine and Surgery of the Navy Department while also serving as a member of the Directing Board of the Procurement and Assignment Service of the War Manpower Commission during a period when the solution of problems of vital importance to the successful conclusion of the war required the intensive and unremitting efforts of all concerned. By his self-sacrifice and the employment of his high professional prestige, his talents as a physician and surgeon, and his abilities for successful organization of professional groups, he rendered the most responsible, notable and distinguished service. To the Navy directly, through his contributions as Honorary Consultant, and to all of the Armed Services through his achievements with the War Manpower Commission, Dr. Paullin's advice and direction were of exceptional and invaluable aid and assistance."

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Major Bain L. Heffner (Associate), Greensboro, N. C., was awarded the Army Commendation Ribbon on August 26, 1946, by Major General Ray E. Porter, in recognition of his "exceptionally meritorious conduct in the performance of outstanding services as Commanding Officer of the 368th Station Hospital, Fort Gulick, Panama Canal Zone."

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Dr. J. C. Geiger, F.A.C.P., San Francisco, Calif., has been honored by the award of the Grand Ducal Order of the Oak Crown of the House of Nassau of the Grand Duchy of Luxembourg, in the Grade of Officer, first class. The decoration was accompanied by the citation, "For distinguished services to the Duchy of Luxembourg and its citizens and as a great humanitarian in the field of public health."

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Dr. Francis R. Dieuaide, F.A.C.P., New York, N. Y., formerly Lieutenant Colonel, (MC), AUS, is the recipient of the Legion of Merit, awarded for his splendid record as Chief of the Tropical Disease Treatment Branch of the Surgeon General's Office, February, 1943, to September, 1945.

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The Legion of Merit has been awarded to Dr. John A. Layne, F.A.C.P., Great Falls, Mont., formerly Major, (MC), AUS. Dr. Layne's outstanding professional and administrative skill in organizing and conducting the Medical Section of the Gardiner General Hospital, September, 1944, to April, 1946, is cited.

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Colonel James B. Anderson, (MC), USA, F.A.C.P., Bradenton, Fla., has been awarded the Legion of Merit for outstanding services, unusual clinical ability and administrative skill, demonstrated in his activities as commanding officer, Ashburn General Hospital, February, 1943, to October, 1945.

Col. Raymond O. Dart, (MC), USA, F.A.C.P., has succeeded Col. James E. Ash, (MC), USA, F.A.C.P., as Director of the Army Institute of Pathology, Washington, D. C.

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Col. Arden Freer, F.A.C.P., has retired from the Medical Corps, U. S. Army, in which he held the position of Chief of Medical Consultants Division in the Surgeon General's office. Dr. Freer served in the Army for 32 years. He is now a member of Dr. Hawley's staff in the Veterans Administration. Col. Henry C. Dooling, (MC), USA, F.A.C.P., formerly Chief Health officer, the Panama Canal, has been appointed to succeed Col. Freer.

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Brigadier General Charles C. Hillman, (MC), USA, F.A.C.P., has retired from the service to become Director of the Jackson Memorial Hospital, Miami, Fla.

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Dr. Edward L. Turner, Dean of the new University of Washington School of Medicine, in Seattle, has announced the appointment of the following as Clinical Professors of Medicine: Edwin G. Bannick, F.A.C.P.; Lester J. Palmer, F.A.C.P.; Charles E. Watts, F.A.C.P. Dr. Roscoe L. Pullen, F.A.C.P., has been appointed Associate Professor of Medicine and Director of Hospital Planning.

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Dr. Victor E. Johnson, F.A.C.P., Chicago, Ill., Secretary of the Council on Medical Education and Hospitals of the American Medical Association, and Professorial Lecturer in Physiology at the University of Chicago, has accepted appointment, beginning in April, as Professor of Physiology in the Mayo Foundation for Medical Education and Research, Rochester, Minn. In October, 1947, Dr. Johnson will succeed Dr. Donald Balfour as Director of the Foundation.

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Dr. James J. Short, F.A.C.P., Los Angeles, Calif., formerly Associate Clinical Professor of Medicine in the New York Postgraduate Medical School, has been appointed Associate Professor of Medicine and Director of the Department of Internal Medicine in the Graduate School of the College of Medical Evangelists.

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Dr. Ralph L. Shanno, F.A.C.P., Forty Fort, Pa., has been elected President of the Mercy Hospital Staff (Wilkes-Barre) for 1947.

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Dr. D. Ward Scanlan, F.A.C.P., was recently elected Medical Director of the Atlantic City Hospital, Atlantic City, N. J.

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Dr. David Scherf, F.A.C.P., New York, N. Y., has been made an honorary member of the Brazilian Society of Cardiology and a corresponding member of the Argentine Medical Society.

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Dr. Albert S. Hyman, F.A.C.P., New York, N. Y., has been appointed Consulting Cardiologist to the Veterans Administration Hospital, Castle Point, N. Y. Following four years of service in the Navy Medical Reserve Corps, Dr. Hyman has prepared for publication a book, "Psychosomatic Heart Disease," based largely on experiences in the combat area.

Officers of the Institute of Medicine of Chicago, elected for the year 1947, include the following Fellows of the College: Dr. William H. Welker, Vice President, Dr. George H. Coleman, Secretary, and Dr. Grant H. Laing, Treasurer. Dr. LeRoy H. Sloan and Dr. J. Roscoe Miller were elected Governors of the Institute.

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Dr. Aaron E. Margulis, F.A.C.P., has been appointed Professor of Bacteriology, Executive Officer of the Department of Bacteriology, and Director of the Hospital and Dispensary Services of Bacteriology in the New York Post-Graduate Medical School and Hospital, following the death of Ward J. MacNeal. At the time of Dr. Margulis's appointment, he held an Assistant Professorship in Pathology in this institution.

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Dr. Frank B. Queen, F.A.C.P., Denver, has been appointed Professor of Pathology at the University of Oregon Medical School, Portland, and director of the state cancer control program, effective September 20. Dr. Queen, who graduated at Washington University School of Medicine, St. Louis, in 1929, has served on the faculties of the universities of Rochester, Pennsylvania, Colorado and Northwestern.

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#### RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to February 13, 1947 inclusive).

Malcolm L. Barnes, Louisville, Ky. (Lt. Col., MC, AUS)  
Benjamin B. Blum, Petoskey, Mich. (Capt., MC, AUS)  
Norman Q. Brill, New York, N. Y. (Lt. Col., MC, AUS)  
George W. Burnett, Oil City, Pa. (Major, MC, AUS)  
Leroy E. Burney, Indianapolis, Ind., (Col., USPHS)  
Walter P. Davenport, Appleton, Minn. (Col., MC, USA)  
Abraham M. Gordon, Louisville, Ky. (Capt., MC, AUS)  
Bain L. Heffner, Greensboro, N. C. (Major, MC, AUS)  
Russell W. Kerr, Kansas City, Mo. (Major, MC, AUS)  
Thomas H. Pargen, Baton Rouge, La. (Comdr., MC, USNR)  
Seymour C. Schwartz, Syracuse, N. Y. (Col., MC, USA)  
William L. Sheep, Washington, D. C. (Brig. Gen., MC, USA)  
Edward T. B. Weidner, Philadelphia, Pa. (Col., MC, USA)

## OBITUARIES

## DR. PAUL PRESSLY McCAIN

The medical profession and the whole State of North Carolina were deeply shocked and grieved over the untimely death of Dr. Paul Pressly McCain in an automobile accident near Raleigh, N. C. on November 25, 1946. Dr. McCain was traveling to Raleigh for a Committee meeting of the North Carolina Medical Society.

Paul Pressly McCain, A.B., M.D., LL.D., F.A.C.P., Sanatorium, N.C. Born, Due West, S. C., June 26, 1884; attended Erskine College and the Atlanta College of Physicians and Surgeons; M.D., 1911, University of Maryland School of Medicine; became affiliated with the North Carolina Sanatorium in 1914 as Chief of Medical Service and Assistant Superintendent and became Superintendent and Medical Director in 1924, an appointment he held to the time of his death; Assistant Professor of Medicine, Duke University School of Medicine, Durham; Diplomate, American Board of Internal Medicine; formerly served as President of his County Medical Society, his State Medical Society, the Southern Tuberculosis Conference, Southern Sanatorium Association, National Tuberculosis Association, and as Director and Member of the Executive Committee of the North Carolina Tuberculosis Association; Member, American Trudeau Society, American Clinical and Climatological Association and the Southern Medical Association; Member of the Sub-committee on Tuberculosis of the National Research Council; was also Superintendent, Medical Director and Director of the Extension Department of the North Carolina Sanatorium for the Treatment of Tuberculosis; Superintendent, Western North Carolina Sanatorium, Black Mountain; Member of the Editorial Board of the *North Carolina Medical Journal*; Trustee, Flora Macdonald College, Red Springs; Fellow of The American College of Physicians since 1924.

It can be said without fear of contradiction that Dr. McCain was the most beloved, the most respected and the most useful physician in North Carolina. His work in the field of tuberculosis was known throughout the world. He combined the science and the art of medicine in the truest sense of the word. His advice and counsel were sought by hosts of people, both within and without the profession. His warm spirit, his deep understanding and his genuine love of his fellowman were expended without stint and he will be deeply mourned and sorely missed by people in all walks of life. Dr. McCain was a credit to his family, his friends, his profession, and his life was a potent influence for good in the affairs of The American College of Physicians. The members of the College in North Carolina deeply mourn his passing and extend the hope that time and a beneficent Providence will eventually afford to his family a measure of comfort.

PAUL F. WHITAKER, M.D., F.A.C.P.,  
Governor for North Carolina



## DR. SAMUEL BARBASH

Samuel Barbash, M.D., F.A.C.P., died suddenly of myocardial infarction on November 14, 1946, at his home, 1902 Pacific Avenue, Atlantic City.

Dr. Barbash was born in Tarnapol, Austria, January 29, 1884, and was brought to this country when nine months old. He attended the Philadelphia Public Schools and received his medical education at the Medico-Chirurgical College of Philadelphia. Upon receiving his degree of M.D. in 1905, he began his medical career by becoming the second interne ever appointed by the Atlantic City Hospital. Thereafter he served the Hospital well and truly until the time of his death, first as Chief of Dispensaries from 1906 to 1911, then as Chief of Medicine from 1912, and as both active Chief and Medical Director from 1935. He saw the Hospital grow from a small cottage of sixteen beds to a three hundred bed, Class A institution. Few contributed as much, none contributed more, to its growth and attainments.

He served as Resident Medical Director of the Jewish Seaside Home for Invalids, and was Consultant in Medicine and Physiotherapist, at the Betty Bacharach Home for Afflicted Children in Longport. He was a Past President of the Medical Society of Atlantic County, and of the Board of Medical Examiners of New Jersey, of which he had been a member since 1939. He was a Diplomate of the American Board of Internal Medicine; member of the Medical Society of the State of New Jersey, Medical Club of Philadelphia, American Medical Association, American Heart Association, and American Association of the History of Medicine. He had been a Fellow of the American College of Physicians since 1929.

He took an active interest in his community and its civic problems; he was a member of the Chamber of Commerce, the Kiwanis Club, and a Mason.

Dr. Barbash was a superior clinician, an able administrator, a constructive citizen and a loyal friend. His counsel was in constant demand by all, but especially by his juniors, and his helping hand contributed much to the professional advancement of more than a few. Much of his ebbing energy was spent in assuring a continued vitality to the Staff of the institution he loved so well, the Atlantic City Hospital, by husbanding and channeling the resources of the returning veterans. Fully aware of his limited cardiac reserves, he curtailed his private practice for months, but continued to give his energy unstintingly to the Hospital as Medical Director and to the State Board of Medical Examiners.

His enthusiasm was contagious. His energy was boundless. His kindly leadership was vigorous and unrelenting. His accomplishments were unsurpassed. His passing has left a rent in the community fabric. Dr. Barbash's impact upon the profession will be felt for years.

HILTON S. READ, M.D., F.A.C.P.

## COLONEL FRANK W. WILSON

Colonel Frank Wiley Wilson, M.C., U.S.A., died on April 20, 1946, of a heart ailment at the Moore General Hospital at Swannanoa near Asheville, North Carolina, of which hospital he was the commanding officer.

Colonel Wilson was born on April 29, 1888, at Greenville, North Carolina. He obtained his medical degree from the University of Maryland in 1914. He was given a reserve commission in the medical service of the Army in August 1915 and, after graduation from the Army Medical School in 1916, he was appointed to the Medical Corps. His first service was on the Mexican border, followed by oversea duty in World War I. Since that time he had three tours of duty at Walter Reed Hospital in Washington and a long period of service at Fort Benning, Georgia. In 1934 he completed the advance course at the Medical Field Service School at Carlisle Barracks. He was placed in charge of the Station Hospital at Camp Shelby, Mississippi, in 1940 and in 1942, when the Moore General Hospital was established, he was assigned to its command and awarded the Legion of Merit in February 1946 for his services at this hospital.

Colonel Wilson became an Associate of the American College of Physicians in 1936, and a Fellow in 1939. He was also a Fellow of the American Medical Association and a member of the Georgia State Medical Society. He was a Diplomate of the American Board of Internal Medicine.

Colonel Wilson is survived by his widow, Mrs. Mary Inez Wilson, and five brothers, among them Major General Durward S. Wilson, retired, Colonel Carl B. Wilson of the Infantry and Colonel Bascom L. Wilson, Medical Corps.

Major General NORMAN T. KIRK, M.D., F.A.C.P.,  
Governor for the Medical Corps, U. S. Army

## DR. PARLEY NELSON

Dr. Parley Nelson (Associate) of Rexburg, Idaho, died September 12, 1946, following a stroke; age, 71 years.

Dr. Nelson was born February 17, 1875; he attended Jefferson Medical College of Philadelphia, receiving his medical degree in 1908.

He was formerly City Physician to Manti, Utah, and County Physician at Sanpete, Utah. He served as internist at the Spencer Clinic at Idaho Falls for some years. He had also been City Physician at Rexburg, Utah. For a number of years he had been a member of the Idaho State Board of Medical Examiners.

He became an Associate of The American College of Physicians in 1926.

## CHICAGO: CENTER OF MEDICAL EDUCATION, RESEARCH AND PRACTICE

MEMBERS of the American College of Physicians who attend the Twenty-eighth Annual Session will find Chicago a center of vital activity in the ever-widening fields of medical education, research and practice. By virtue of its fine tradition and heritage, this city, situated on the plains of the Great Lakes, may well become the medical capital of the world.



The Palmer House, General Headquarters  
Twenty-Eighth Annual Session

Chicago is the site of four class A medical schools, one of them first and another third in enrollment among sixty-nine medical schools last year. It is the only city in the world with three internationally known dental schools. This city is the home of a dozen national and international organizations active in medicine and related fields, the site of the world's largest general

charity hospital, the center of medical publishing and medical libraries, a pioneer in atomic medicine, and the home of the world's largest medical society.

Among these organizations are the American Medical Association, the American College of Surgeons, the American Association of Industrial Physicians and Surgeons, the American Dental Association, the American College of Chest Physicians, the American College of Radiology, the American Congress of Physical Therapists, the Association of American Medical Schools, the American Association of Allergists, the American College of Hospital Administrators, the American Hospital Association, the American College of Nurse Anesthetists, and the American Association of Medical Record Librarians. The American Medical Association has 128,000 members; its nine-story building houses some 600 employees; and on its own presses each week some 45,000 tons of paper become journals, books, charts, pamphlets and posters which circle the globe.



The American Medical Association

Chicago's own medical society, with 7,000 members, is the largest city medical group in the world. The medical schools of the University of Chicago, the University of Illinois, Loyola University, and Northwestern University have graduated 10,616 physicians between the years of 1928 and 1946.

While it is not possible to list here all of the seventy-six hospitals of the Chicago area, it is impossible to omit mention of one of the greatest of civilian hospitals ministering to the needs of Chicago's increasing population, manned by teachers from the medical schools, all serving without pay—Cook County Hospital. Here is afforded a wealth of clinical material, and here many of the outstanding physicians of the country served their internships. Here also, in days gone by, the Illinois Training School for Nurses trained and sent into service thousands of women, many of them to high executive and teaching positions in the hospital and nursing world, a work now taken over by the Cook County School of Nursing.



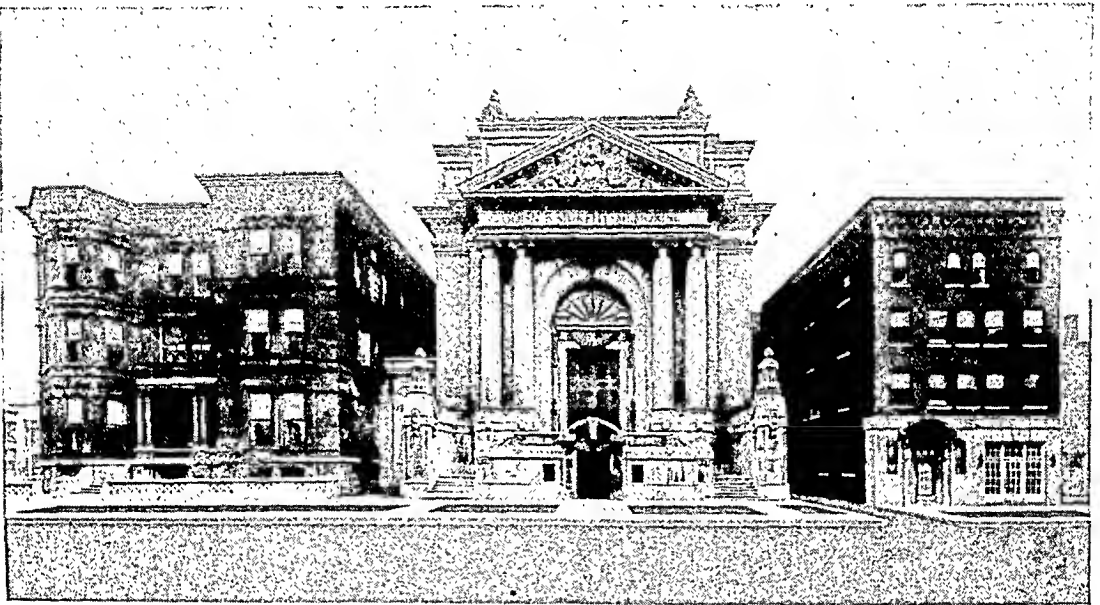
Cook County Hospital

Chicago, which has more general libraries than any other city in the world, also ranks high in its medical libraries; Billings Library at the University of Chicago, the Archibald Church Library at Northwestern University, those at Loyola University and University of Illinois, and the Crerar Library accessible to all in Chicago's loop. All of the major hospitals have libraries for the quick reference of their staff members.

Rush Medical College began instruction in two rented rooms in December, 1843. It had been chartered by the General Assembly of the State of Illinois in February, 1837. Rush Medical College held the first charter for

an institution of learning granted by the legislature of the State of Illinois; this was the oldest charter under which any school of any kind was in operation in Illinois. In the year this charter was granted, Chicago was an active, vigorous community of 3,000 people.

Daniel Brainard had journeyed to Chicago from New York State where he had spent two years with a preceptor in Whitesboro, New York. He had then studied for a year at the medical college in Fairfield, New York, and spent 1834 at Jefferson Medical College. Thus, Rush Medical College was in a way intimately linked with the home city of Benjamin Rush, signer of the Declaration of Independence, Professor of the Theory and Practice of Medicine at the University of Pennsylvania.



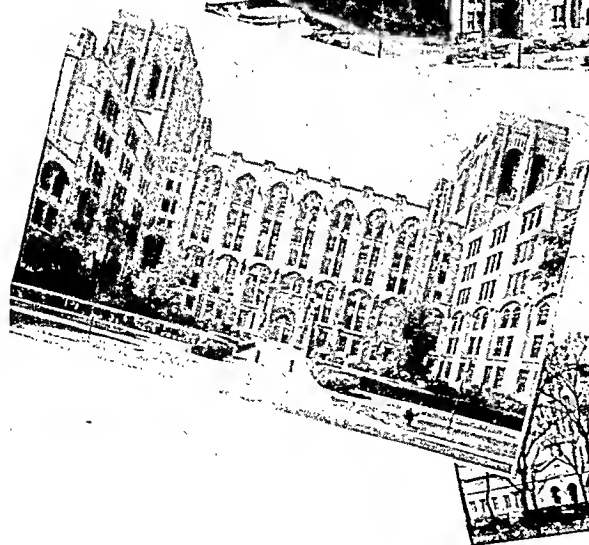
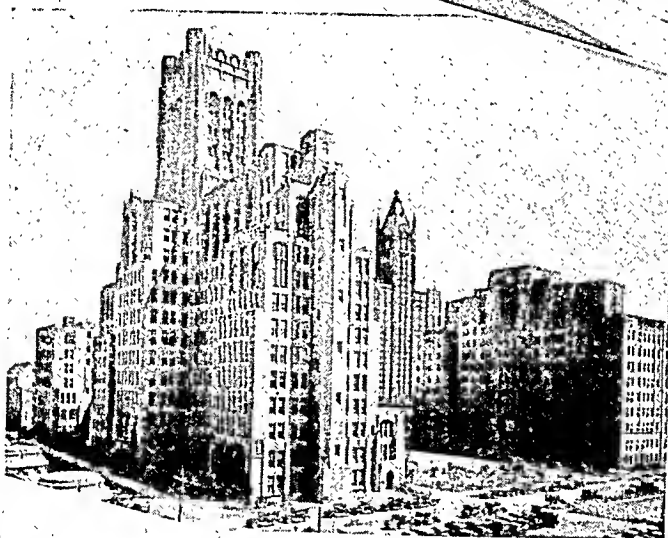
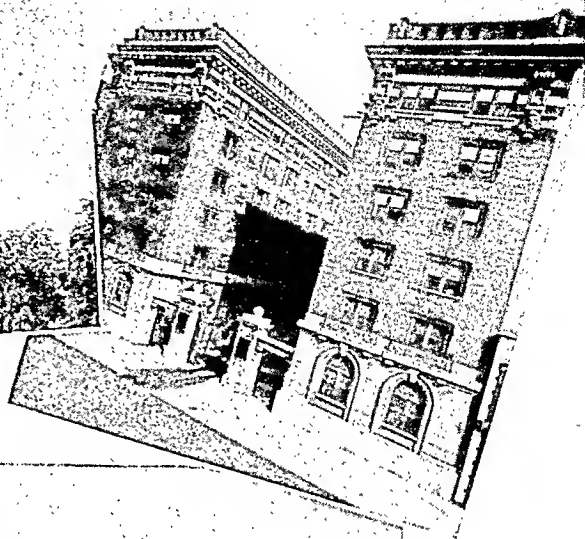
American College of Surgeons group, showing main building (left); John B. Murphy Memorial (center); and Surgery, Gynecology, and Obstetrics building (right)

In 1843, to obtain the degree of Doctor of Medicine it was necessary for one to have had three years of study with a so-called "respectable" physician and two courses of lectures at Rush. The regular fees amounted at that time to sixty-five dollars and the graduating fee was twenty dollars. Austin Flint lectured to the students during the second course of lectures. In 1849 Dr. Nathan Smith Davis came from New York City to teach physiology and pathology at Rush. Dr. Davis was later to be known as the "Father" of the American Medical Association and its founder. Ten years later, as a result of certain changes in policy, Dr. Davis left Rush to become one of the founders and the first Dean of the Medical Department of Lind University, later known as the Chicago Medical College and still later as Northwestern University. The original Lind Block on the northwest corner of Randolph

Street and Wacker Drive is still standing. From 1898 to 1941, Rush Medical College was affiliated with the progressive young University of Chicago; guided by vigorous William Rainey Harper and, in later years, by the challenging Robert M. Hutchins, this school was destined to take a leading position in the advancement of education. Until it closed its doors as an independent institution and became affiliated with the University of Illinois in 1943, Rush was always in the vanguard of progressive medical instruction and reflected the personalities of many great men of medicine: Billings, Senn, Haines, Bevan, Sippy, Herrick, and many others. Meanwhile, the University of Chicago's Medical School developed its philosophy and resources until today, provided with ample facilities for teaching and investigation, it stands as the only medical school with an entirely full-time faculty.

In 1876 Dr. Charles W. Earle formulated plans for the establishment of a College of Medicine adjacent to the Cook County Hospital. Five years later arrangements were made to bring these plans to fruition and on September 26, 1882, the regular sessions of this college began with 100 students. Ten years later a well equipped laboratory building was added to the college property. It is reported that this laboratory structure was the first of its kind in Chicago, and the first one erected by a private medical institution in the United States. In 1896 the Governor of the State of Illinois, John P. Altgeld, entered into discussion with the famous Dean of this school, Dr. William Quine, with a view to affiliation; and, on April 21, 1897, the property was leased to the University of Illinois for four years. On May 1, 1900, the College became officially designated as the College of Medicine of the University of Illinois. Since then the University has grown by leaps and bounds until today it occupies blocks of ground, with large buildings for the care of patients with medical, surgical, neuropsychiatric and special diseases. It is now about to begin a huge program of expansion.

It has been said that Northwestern University was the first medical school in the United States to apply the principles of scientific pedagogy to the teaching of medicine and surgery, and the first school to have a graded course of study. This school was founded as the result of the application of Lind University for affiliation with a medical school. Dr. Hosmer Johnson, Dr. Edmund Andrews, Dr. Ralph Isham, and Dr. Rutter received the full approval of those in control of Lind University to apply the progressive reforms and suggestions for medical education proposed and vigorously supported by Dr. Davis, and in turn invited Dr. Davis and Dr. William H. Byford from the Rush faculty to join in founding a medical department for Lind. On October 9, 1859, the first annual college term began. In his introductory remarks, Dr. Davis made the point, "that the establish-



# GROUP I. (Chicago Hospitals)

Top left, Wesley Memorial Hospital

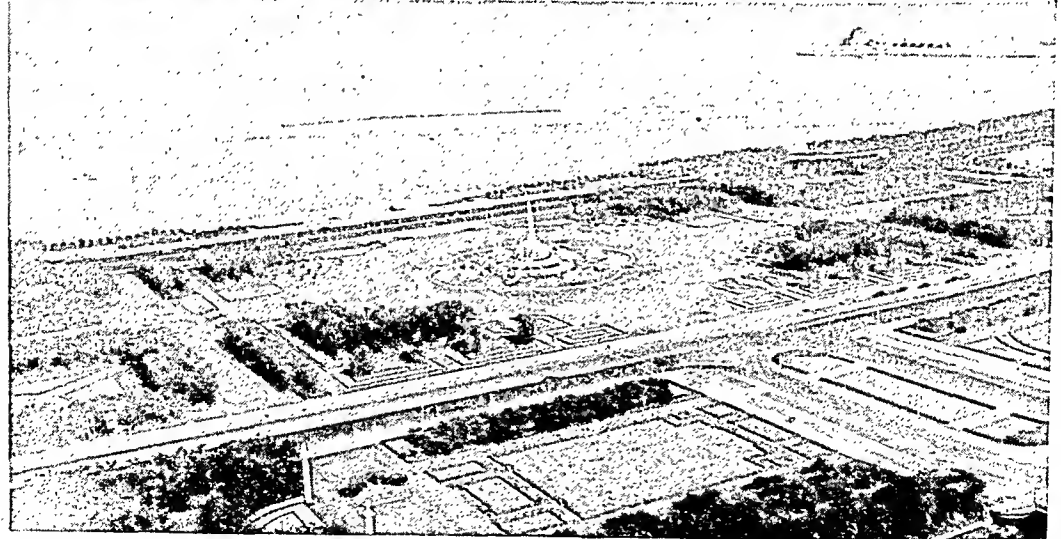
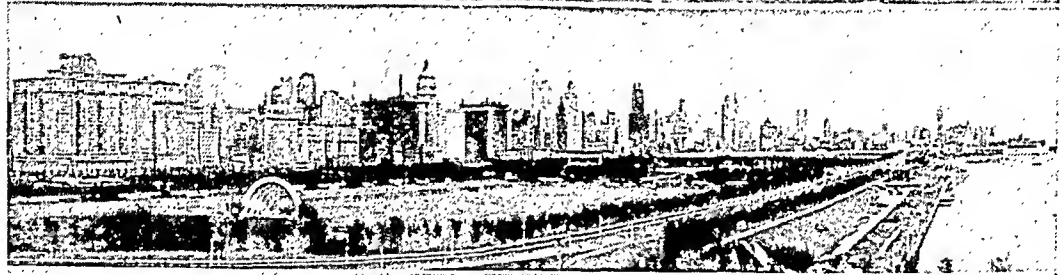
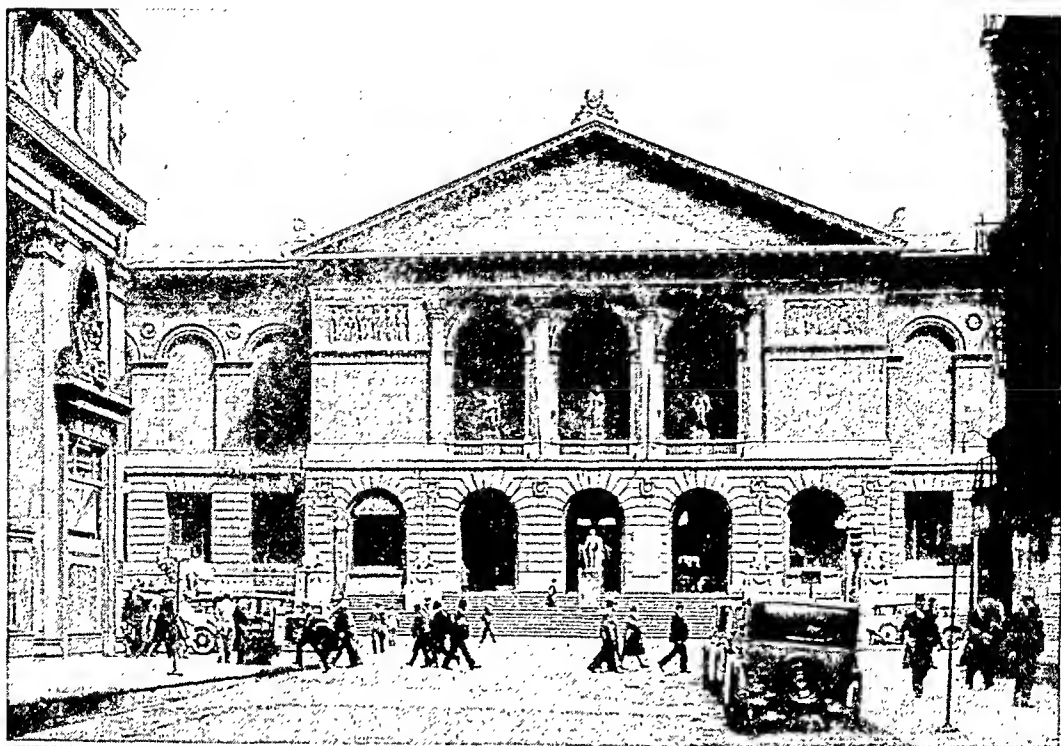
Top right, St. Luke's Hospital

Center, Northwestern University Medical School  
and Passavant Memorial Hospital

Bottom left, Albert Merritt Billings Hospital

Bottom right, Chicago Lying-In Hospital





## GROUP II. (Chicago Views)

Top, The Art Institute of Chicago

Center, Chicago sky-line, looking north along Grant Park

Bottom, Buckingham Fountain (center) ; Lincoln Monument (left foreground) ;  
Adler Planetarium (right background)

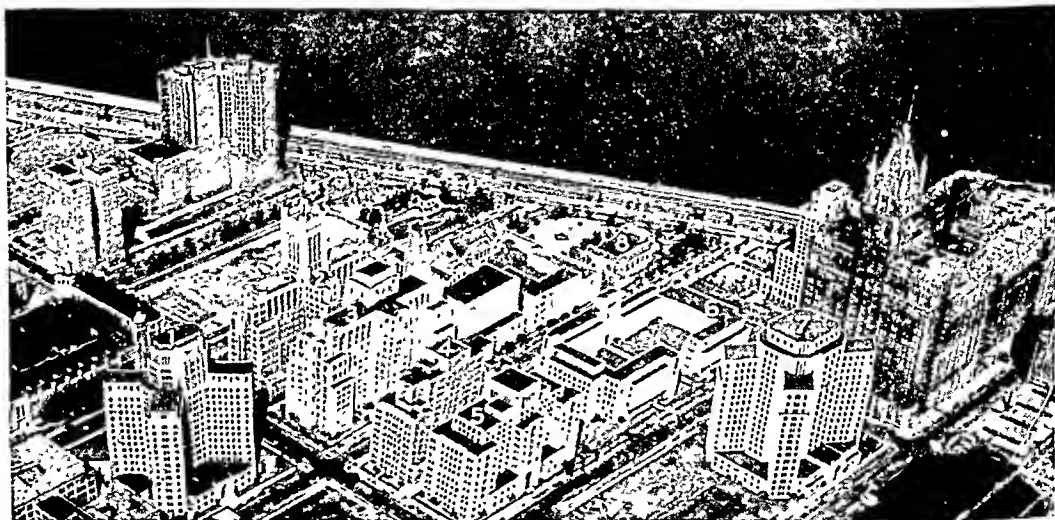
ment of this institution was partly as a result of a sincere desire on the part of the faculty to put into practical operation a system of medical college instruction more in accordance with sound educational principles and better adapted to the present state of science and art of medicine than that which has been so long adhered to by the medical schools of the country." As a result of the inevitable financial changes coming in the wake of war, Lind University released its medical faculty and they in turn opened the Chicago Medical College in October, 1863. Six years later the Chicago Medical College became affiliated with the medical department of Northwestern University.

So much for the past and the present. Plans of giant medical installations, some of them far beyond the blue-print stage, indicate an even greater focussing of medical education and research in the future. A vast monument to healing will be erected in the area bounded by Congress Street, Roosevelt Road, and Ashland and Oakley Boulevards. New buildings planned for this site by the University of Illinois include a general hospital, nursing home, library, museum and dormitories; by the State Department of Public Welfare, hospitals for the aged and chronically ill, maternity cases and mental patients; a 1,000-bed hospital by the Veterans Administration; and a \$5,000,000 medical-dental building by Loyola University. These, plus the thirteen existing institutions which include the new Illinois Neuropsychiatric Institute, the Bacteriological Laboratories of the State Department of Public Health, the Illinois Research and Educational Hospitals, and the Presbyterian Hospital, will constitute a medical center equipped to deal with every phase of medical education and research. "The three-fold goal of this undertaking," said Medical Center Commission officials, "is to preserve and restore health, to seek the cause and cure of disease, and to educate those who would serve humanity."

Chicago's four medical schools, in addition to the classical courses of medical instruction, are pioneering in different phases of medical research. The University of Chicago, less than two months after the atomic bomb was dropped on Hiroshima, projected an Institute of Radiobiology and Biophysics to study the use of radioactive substances in the treatment of disease. There, through the use of isotopes, investigators will be able to study the life processes of plants and animals with minute accuracy. To house its Radiobiologic Institute, as well as allied institutes of nuclear and metal studies, the University will build a \$5,000,000 set of buildings on the campus. The Goldblatt Cancer Hospital will also be added to this University's campus. The University of Illinois' activities are built around their large Research and Educational Hospitals, the Neuropsychiatric Institute for the study of nervous and mental diseases, the Institute of Juvenile Research

—first child study clinic of its kind—plus the extensive facilities of Cook County Hospital. Planned to supplement its work are a \$4,000,000 addition to its hospital, a building devoted to aviation medicine, and a cancer clinic, equipped with the powerful new betatron developed in its downstate campus at Urbana.

Loyola University has trained one of every four practicing physicians in the city of Chicago. Together with her sister medical schools, Loyola is planning increased facilities for the future. A modernistic \$5,000,000 building will enable the school to train 400 medical and 400 dental students at the same time. The expansion program of Northwestern University will require the spending of from \$95,000,000 to \$150,000,000 within the next two decades. In addition to their present medical building, and adjacent Wesley and Passavant Memorial Hospitals, there are proposed a neuropsychiatric clinic, a school of nursing, a urological institute, a children's hospital, a university clinic, and an addition to the general hospital. Some of these buildings will be completed when the University celebrates its 100th Anniversary in 1951. Adjacent to this development of Northwestern University will be the new Mercy Hospital. Mercy—the oldest hospital in Illinois—treated Civil War casualties under its original name of Illinois General Hospital of the Lakes. Plans call for a twenty-two story hospital with a 500 bed capacity, together with nurses' home, chapel, auditorium and convent; estimates of the total cost are about \$10,000,000.



Northwestern University Medical Center  
(Showing existing and proposed buildings)

- |   |   |
|---|---|
| 1. Wesley Memorial Hospital                   | 5. Proposed new hospital                                |
| 2. Ward Building (medical and dental schools) | 6. Proposed cancer and associated clinics               |
| 3. Proposed institute for medical research    | 7. Veterans Administration Hospital (to be constructed) |
| 4. Passavant Memorial Hospital                | 8. Thorne Hall  |

Unique in hospital planning, Michael Reese Hospital, in coöperation with neighboring industries, labor groups, religious and social agencies, has set up the South Side Planning Board which will undertake the redevelopment of the area contained in the rectangle within Twelfth Street, the Pennsylvania Railroad tracks, Forty-seventh Street and Lake Michigan. This area will be completely redeveloped, and about the present hospital building will be a "campus," comprising a number of structures, including a 200 bed private and semi-private pavilion, the nucleus of a new hospital, a psychiatric and psychosomatic institute with extensive laboratories, and a convalescent hospital.

The medical exhibits in the Museum of Science and Industry, located in Jackson Park, represent a coöperative enterprise between the medical schools, medical associations, dental, pharmaceutical and hospital groups. They portray in graphic visual fashion the fundamental structure, function and derangements of the human body. Since the close of the Century of Progress in 1934, these exhibits have served an extremely valuable function in health education, especially in the public and parochial schools of Chicago and neighboring cities. Annual visits to the number of 1,250,000, including 400,000 school children on especially assigned field trips, indicate the tremendous value of these exhibits in the study of health. Various medical associations of Chicago and the State of Illinois have sponsored health lectures in the museum's main theater, and these are well attended. During the war special educational field trips of students from Fort Sheridan and the Great Lakes Naval Training Station aided in the education of men in the armed forces of this country and Canada.

Other institutions, although not connected with the four medical schools, are adding, each in its special field, to the combined total of medical research



Henrotin Hospital

done in Chicago. Among them are the Hektoen Institute, the McCormick Institute for Infectious Diseases, now part of Cook County Hospital, and the Institute of Psychoanalysis. The Chicago Institute of Medicine sponsors annually a series of lectures which draws medical men from distant points.

This brief review of the outstanding institutions of medical education and research is incomplete. It is hoped, however, that it will serve as a quick "tour." Every institution and group will welcome you during your stay here. Perhaps you, too, will leave feeling that Chicago is on the way to becoming the medical capital of the world.

Note: The kindness of the *Chicago Daily News*, in granting permission to use in this account certain information contained in articles by Arthur Snider which it published, is gratefully acknowledged. The source of many of the statements concerning Chicago's past medical accomplishments is the "History of Medicine and Surgery and Physicians and Surgeons of Chicago," endorsed and published under the supervision of the Council of the Chicago Medical Society by the Biographical Publishing Corporation, Chicago, Illinois, 1922.

# ANNALS OF INTERNAL MEDICINE

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## PHYSICIANS OF THE MACHINE AGE\*

By DETLEV W. BRONK, *Philadelphia, Pennsylvania*

HUMANITY has entered a new era. As we speak of the Bronze Age or the Iron Age, we must today speak of the Machine Age. André Siegfried, the distinguished French political philosopher, has recently reminded us that Europeans are disposed to call it also the American Age. For, if it was in Europe that the principles of modern large-scale production were conceived, it was in the United States that they were first put into practice completely and whole-heartedly. This places heavy requirements of leadership on the American people for shaping the human consequences of this new era; it makes unique demands upon the American physician.

The physical sciences and technology which have created this machine age have altered profoundly the task of the physician. They have faced him with new and challenging responsibilities. Fortunately, the achievements of the physical sciences have enabled modern medicine to meet this challenge more effectively. From chemistry and physics the medical scientist has gained knowledge and instruments for his own spectacular discoveries in the cause and cure of disease. Technology has made possible our organized efforts for the treatment of human ills.

Through organic evolution—slowly acting over countless centuries—man acquired his natural powers; he became adapted to a limited environment. Gradually he learned to supplement curiosity with the powers of observation and reason and association. Finally, with the advent of the Baconian era of experimental science he developed special technics for unravelling the causes of things, so that he might establish conclusions “useful for man’s life and knowledge.” Thus man has extended his natural powers.

Among the first fruits of that scientific era came clearer understanding of the nature of our bodies and of the relation of our life to our environment. The microscope revealed the structure of the living organism for the care of which the physician is responsible. Machines for the production of

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\* Convocation address, Twenty-Seventh Annual Session, American College of Physicians, Philadelphia, May 15, 1946.

roentgen-rays disclosed the interior of the body and created a new epoch in diagnosis. Electronic amplifiers now make it possible to observe the subtle functions of the nervous system and to probe the mysterious workings of the brain. The electron microscope brings viruses within the range of human vision. The cyclotron and the atomic pile which gave us a new, dread agent of destruction also provide radio-active elements with which to trace the chemical processes of life.

These are but a few examples of how the machines of our scientific age extend the sensitivity and the range of human senses. By such devices we have established an entirely new sensory relationship to our environment. These instruments have broadened the intellectual horizons of man. They have enabled the physician to understand more fully the mechanisms of the body. Because of that he has been able to aid men to resist more effectively the invisible agents of disease—to aid men to meet more adequately the forces of their environment.

These forces are no longer merely natural in origin. Through instrument-aided senses the scientist has gained a clearer insight into nature. Thus he has been stimulated to the invention of new machines for human power. By these our voice is carried around the world. The power of a hundred thousand horses is held under the control of a finger—capable of releasing men from the bondage of labor. Machines carry us swiftly across the land, under the sea and through the air. By machines we have created our own environments, without regard for natural heat or cold, and light or darkness.

It is not my purpose to recount the brilliant, but familiar, achievements of modern science. It is my purpose to emphasize the biological usefulness of scientific effort. It is to remind you that the curiosity of scientists will continue to create new conditions, amidst which the lives of men must be lived. If physicians do not direct the course of our machine age, so that it satisfies more perfectly the biological needs of men, I must ask you: Who is there capable of doing so?

Machines should be created for the aid of men. If they have any useful function, it is to increase the natural powers of the human body. Unfortunately, engineers know little of how the body works and physicians are unable to design machines. Because of this dichotomy of social functions, the biological basis of machines has been generally ignored, and life has been less wholesome than it might have been.

These problems were brought into sharp focus by the needs of war. Out of our common peril there was reborn respect for men and their biological needs. Machines assumed their proper rôle as instruments for their users rather than as mere objectives of an industrial civilization. It was then quite obvious that gun-sights and bomb-sights are aids to vision; that submarines are devices for sustaining life below the seas; that aeroplanes were created to give men the power to travel swiftly in three dimensions. To achieve these purposes more effectively, physicians and engineers formed

a natural partnership. In the Armored Forces Medical Laboratory, in the Naval Medical Research Institute and in the Aeromedical Laboratory of the Army Air Forces Material Command physicians studied the biological suitability of instruments and machines. New designs were guided by the physicians' knowledge of the mechanisms and the requirements of the human body. Under their direction, anthropologists adapted the dimensions of seats and turrets and controls to the structure of the body as well as to the convenience of the engineer. Physiologists and ophthalmologists designed lighting systems for boats and tanks and planes so as to protect night vision. Pathologists re-designed structures responsible for injuries in crashes.

Out of this close partnership also came a clearer realization that new powers provided by machines may place new stresses on the body. There are three clear instances of this in the spectacular advance of aviation.

The history of this advance is a long record of man's restless urge to overcome his physiological restrictions. It first appears in mythology and ancient literature as a desire for the birds' freedom from the gravitational tie to earth. But when in 1783 man was at last freed from his earth-bound life he was only started on the conquest of his aerial limitations.

Driven by the urge for greater range of action, man's mechanical ingenuity devised means for ascent to ever higher altitudes—to which he had not been adapted by the slow process of evolution. Finally in 1862, Glaisher, an English meteorologist, and Coxwell, his balloon engineer, reached the limits of human survival. They went to a reported altitude of over five miles. There Glaisher became unconscious and both would have perished, had not Coxwell, paralyzed though he was, seized the valve cord in his teeth and released the gas by vigorously nodding his head. On recovering consciousness, Glaisher voiced man's faith in the power of science to break the bounds of human limitations: "I certainly shall not take it upon myself," said he, "to set the limits of human activity and indicate the point, if it exists, where nature tells the aeronaut: 'You shall go no further'."

I have retold this classic account of a physiological limitation on the use of aerial machines because it was overcome by a medical scientist. By studying the reactions of the human body to high altitudes Paul Bert found that unconsciousness and death are there due to a lack of oxygen. From then until now, physicians have been partners in the development of high altitude flight by following in the footsteps of Paul Bert and prescribing the oxygen necessary for life.

This was one of the major functions of the medical services of the air forces during this war. Each airman was carefully instructed in the physiology of high altitudes. The medical services designed modern equipment that would deliver enough oxygen to meet the fliers' needs at any height. Physicians carefully watched the aerial operations for signs of harmful effects on the personnel. Engineers and physicians together made it possible for our airmen to fly their great bombing missions over the Nazi's European fortress.



Ultimately the skill of engineers threatened new hazards to the body. Anti-aircraft fire reached higher; but engine superchargers met the challenge, and carried our planes still higher. Finally, at 38,000 feet the pressure of the atmosphere becomes so low that even pure oxygen delivered to the lungs was not sufficient adequately to load the blood. There life became impossible. Machines had once again exceeded the physiological powers of those for whom they had been constructed. Once more physicians and engineers pooled their knowledge, and the pressurized cabin was created. In those sealed enclosures, air compressed to give the airmen adequate oxygen and warmth. In those machines a natural environment has been restored to fliers, at altitudes unsuitable for life.

Two of the primary requirements for good fighter-craft are high speed and great maneuverability. These are the characteristics which enable them to excel in plane-to-plane combat, to evade the heavier fire-power of larger craft, and to give effective protection to bomber missions. Engineers and metallurgists worked for years to develop such planes that can withstand the centrifugal forces of high-speed turns and the pull-out from a power dive.

The engineers succeeded, but the machines they created could not be flown by men. For our cardiovascular system was not evolved to pump blood made five to ten times as heavy by a suddenly applied centrifugal force. Under these conditions, blood accumulates in the lower extremities and in the viscera. The result is an inadequate supply of oxygen to the brain. Gray-out, then black-out of vision are the first effects, and loss of consciousness follows. To help the human body meet these stresses imposed by swift combat planes, physicians designed anti-acceleration suits which aid the heart, by preventing the pooling of blood in the lower parts of the body. Without such a device the engineers' creation is but a futile object, unsuitable for use in the hands of a blind or unconscious pilot.

Artificial wings and powerful motors have freed men from the age-old restriction of gravitational forces. But the new machine forces act upon the body of the pilot as well as upon the artificial wings. The force which holds the plane in a banked turn, or in a loop, excites the gravity receptors, the tension receptors in the muscles and the tendons, and the nervous endings in the semicircular canals which detect rotation. These sensory pathways are then stimulated by the resultant of this machine-exerted force and that of the earth's gravitational field. Because the sensory mechanism is unable to resolve these two components of the stimulating force, a true sense of orientation in space is lost. The false sense of position must then be corrected by visual reference to the earth. And so, when clouds or darkness interfere, the pilot becomes incapable of maintaining a desired course relative to the surface of the earth. That was all that could be said about the matter in the first World War.

Finally, however, physicians determined the causes of man's inaptitude for directed flight without visual contact with the earth. It was then possible to devise instrumental aids and flight through clouds and darkness

became safe and commonplace. Once again the physiological characteristics of the flier had limited his full utilization of his aircraft; once again physicians defined the need and physicists provided instruments to supplement the senses. By the artificial horizon and the bank-and-turn indicator and by radar the machine was adapted to man and the scope of human flight was once again increased.

What we have done to adapt the machines of war to the needs of those who fought in our defense can be done for the machines of peace. We are probably at the beginning of an era of great scientific and industrial development. It will be a human tragedy if physicians and biologists do not sit in the councils of those who shape the instruments and the environments of man. All about us we can see the unhappy consequences of a great industrial civilization, created without adequate regard for the biological requirements of physical and mental health. Millions who come together in cities to use the machines of industry live under the pall of an unnatural atmosphere polluted by the products of the machine. Death stalks the highways at night in high-powered vehicles illuminated with disregard of the facts of vision. Machine-made noise is the constant lot of those who cannot escape to a more natural environment. But these are not necessary faults of the machines—for machines are as we make them. We can build them for our use or for our harm.

Physicians, who understand the variability of individuals, realize that it is impossible to design machines which satisfy equally well the needs of all men. This is especially true of the complicated tools of modern industry. The use of specialized machines requires special qualities of body and mind. It thus becomes necessary to fit men to machines as well as machines to men.

After physicians and engineers had done the best they could to design the machines of war for the men who must use them, physicians selected the men who were best suited to the machines. By visual tests, night fighter pilots were separated from day fighters; on the basis of their physical characteristics, submarine crews were differentiated from the crews of surface craft; a low tolerance of anoxia disqualified a man from high altitude flying; and poor physical fitness removed a soldier from an armored tank to non-combatant service.

The machines of industry are likewise suited to various types of human organisms. The rolling mill in a steel plant and the typewriter in an office are both useful tools. But a man who can manipulate the typewriter may be quite unable to operate the rolling mill. Or the manual dexterity required to drive a truck is inadequate for a tool-maker. The ingenuity of the engineer will surely increase the number and variety of machines. They will frustrate men or they will increase his powers for useful achievement, depending upon how effectively the physician selects those who are physically qualified for their operation.

The diversity of machines also provides a remarkable opportunity to the physician who is concerned with the physical and mental rehabilitation of

those who have lost some of their normal physiological powers. If machines can be designed to give the average man undreamed of ability to travel with the speed of sound, or see across the oceans and blast apart the mountains, surely it is not too much to hope that the maimed and weak can be equipped to play a useful rôle in modern industry. Among the diversified machine operations of the future there can be some machine-suited to the physical ability of each worker. Instruments and machines can overcome the broken body's limitations and restore the patient's usefulness and self-respect. This should be a powerful aid to the physician in the care of the sick and wounded. To achieve this objective, we must have the understanding coöperation of engineers and industrialists—and the directing wisdom of the physician.

Gloomy prophets of the machine age have long predicted that work would become a mechanical round of monotonous boredom. We must admit that some of the joy of craftsmanship has been lost, but we cannot deny that many are being freed from dull, debasing labor. Galley-slaves and those who toiled from dawn to dusk to build the pyramids have been replaced by skilled operators of machines. But the machines are useful only to those who have the necessary skills and mental fitness. With increasing specialization in modern industry, there is, accordingly, a growing need for the selection of those who are psychologically suited to each special task.

Some industries have proved the profit of this practice. But it was under the compelling stimulus of a machine war that the medical service of the Army Air Forces gave the clearest demonstration of its value. Physicians combined physical and psychological examinations in an over-all assessment of the fitness of an individual. Selection was first made of those best suited for duties on the ground or in the air. From among the latter, men were then chosen for the several special tasks of pilot, bombardier, navigator, gunner. The results were remarkable. In the case of one large control group their assessed fitness was disregarded and they were assigned to a duty by chance or preference. At the end of their training it was found that those who would have been excluded from duty as a pilot had three times as many accidents as those who would have been assigned. Furthermore, of those who had been judged to be best qualified for their duties only 4 per cent were disqualified for poor performance in their work. On the other hand, 80 per cent of those who would have been barred from training were ultimately "washed-out" on the basis of poor achievement. Such was the proof that it is possible to avert the prevalent human wastage of square men in round machines.

Democracy demands freedom in choice of occupation. But the success of an industrial democracy requires also that the worker shall have expert guidance in his choice of that occupation for which he is mentally and temperamentally fitted. A misplaced worker cannot use his machine to good advantage, and society is the loser.

The direct impact of machines on men in war and industry is but one aspect of a changing pattern of life in the machine age.

Science frees men from the hazards of ignorance and the uncontrolled domination of natural forces, but science and technology also create a complex civilization that severely taxes the biological capacities of the individual citizen. Each new scientific discovery that provides men with new powers creates new human problems and new dangers. We cannot, and we would not, retreat out of the scientific civilization we have created, and we cannot stand still. Either we will increase our understanding of the forces which shape our lives, and use them to our advantage or we shall fall victims to uncontrolled powers.

Scientific discovery is the exploration of the unknown, and I, for one, do not see how it is possible to direct an explorer through unknown territory. Because of this no man can plan or predict the future of civilization. But it is possible to modify its course and shape new developments to the benefit of men. The internal combustion engine that carries bombers on their missions of destruction is the same engine that cultivates the fields for starving millions. The slums of modern cities blight the lives and dwarf the spirits of men. But the same machines that build the slums can recreate the cities for human welfare. The aerial transportation that makes more difficult the control of epidemic diseases is also available for the swift transportation of sick and wounded.

The machine age will be as we make it. Science gives us the building stones of a better world. If our primary concern is for the machine and the power of machines, it will be a world in which flesh and blood are less real than paper and ink and celluloid and steel.

The blast of the atomic bomb awakened men to an awareness of the human implications of the forces controlled through science. The time is ripe to supplement the generous instinct for human welfare with aggressive action by those who are familiar with the biological needs of men. Only thus will it be possible to give men a life of usefulness and purpose—with machines as their tools for biologically and spiritually significant accomplishments.

For this great humanitarian task of fitting the Machine Age to the biological needs of men there is no one better fitted than the physician.

# RHEUMATIC PNEUMONIA \*

By DONALD W. SELDIN, HENRY S. KAPLAN, and HENRY BUNTING,  
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## INTRODUCTION

THE interpretation of pulmonary lesions in rheumatic fever has had a complex history. Originally the lung had been considered, on clinical grounds, to be one of the major foci of rheumatic activity; the discovery of a primary lesion in the heart, together with more careful pathological study of the lungs, has led to the realization that in many cases the lesions previously diagnosed as rheumatic pneumonia were actually due to cardiac failure or to such complications as infarction, atelectasis or intercurrent infection. In some quarters the pendulum has swung completely in the other direction and the existence of a pulmonary component of the rheumatic process has been categorically denied.<sup>7</sup> Nevertheless, careful investigations by a number of different observers<sup>20, 19, 21, 9, 13, 18</sup> have led to the recognition of a characteristic pathological picture which is not attributable to any of the above-mentioned complications and occurs only in the presence of rheumatic activity. Although the term "rheumatic pneumonia" has been assigned to this pathological condition, its precise relationship to rheumatic fever is still obscure.

At least four hypotheses may be advanced to explain the etiology of this process. Some workers<sup>8, 9</sup> feel that the lesions observed are specific manifestations of rheumatic activity in the lungs, just as Aschoff bodies represent rheumatic activity in the heart. Indeed, Gouley and Fraser have reported the presence of Aschoff bodies in these pulmonary lesions—an observation not confirmed by a number of other investigators. Furthermore, the individual lesions regarded as specific (alveolitis, mononuclear infiltration, hyaline pseudomembrane, etc.) have since been recognized as the common expressions of a variety of distinct pathological conditions. In the light of this work, the thesis that rheumatic pneumonia is a specific manifestation of active rheumatic fever remains unproved on the basis of available pathological data.

The possibility that the pulmonary changes are purely secondary to congestive heart failure constitutes a second hypothesis. Epstein and Greenspan<sup>4</sup> have carefully investigated this possibility and found, in 23 cases of acute and chronic coronary arterial disease in which death was due to cardiac failure and in 16 cases of hypertensive heart disease with failure, that "the only changes in the lungs were chronic ones characteristic of long-

\* Received for publication July 9, 1946.

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standing pulmonary congestion." That the presence of mitral stenosis does not confer this characteristic picture upon the pulmonary manifestations of congestive heart failure is indicated by the fact that these investigators found no hyaline membranes in the lungs of 20 cases of mitral stenosis in which death was due to unrelated causes or to chronic heart failure. It seems, therefore, that cardiac failure per se, even when associated with chronic valvular lesions, cannot account for the anatomical features which have been labeled rheumatic pneumonia.

It is highly unlikely that intercurrent infection during the course of rheumatic fever is responsible for these pulmonary changes: pathogenic organisms cannot be isolated from the sputum; the roentgen-ray appearance is diffuse rather than segmental; and the clinical picture is not typical of bacterial pneumonia.

Finally, it has been suggested that a *combination* of rheumatic activity and cardiac failure might be responsible for the pathogenesis of the lesions. Hadfield<sup>13</sup> concluded that the primary lesion of the rheumatic lung is a "widespread fibrinous alveolitis," which may be *converted* in the presence of dyspnea, probably of cardiac origin, into the characteristic pattern of rheumatic pneumonia. Epstein and Greenspan ascribe this pattern to a combination of diffuse rheumatic vasculitis and dyspnea, most likely due to heart failure.

There is good general agreement concerning the pathological features of rheumatic pneumonia, even though the etiology of these lesions is undetermined, but the clinical manifestations of this condition are still the subject of controversy. The object of the present study is to establish criteria by means of which a clinical and roentgen-ray diagnosis of rheumatic pneumonia might be ventured.

## REVIEW OF THE LITERATURE

### I. *Pathological*

The older literature on rheumatic pneumonia has been reviewed by Paul,<sup>23</sup> Howard<sup>14</sup> and Epstein and Greenspan.<sup>4</sup> Most of the reports prior to 1920 were not accompanied by autopsy verification and therefore cannot be evaluated. Within the last two decades, a more precise investigation of the pathology has resulted in a fairly well-established anatomical description of the disease. Only the major contributions to this description will be noted here, as exhaustive reviews of the pathological literature have been made by Epstein and Greenspan<sup>4</sup> and Neubuerger, Geevër, and Rutledge.<sup>22</sup>

The gross picture has been stated by many observers<sup>20, 12, 18, 11, 19</sup> to be characteristic. The lung has an "india rubber-like," resistant consistency and its surface is mottled with focal hemorrhages. More reliable criteria for diagnosis, however, are the microscopic features, which may be considered under five main categories:

(1) *Alveolar walls and interstitial tissues.* Naish<sup>21</sup> described thickening of the alveolar walls by the proliferation of endothelial cells, some fibroblasts, and occasional polymorphonuclear leukocytes. This is a constant feature of the disease which has been observed by all investigators. Engorgement of the capillaries has also been repeatedly noted. Gouley<sup>11</sup> stressed the edema of the interstitial tissues in the early phases. In studying the evolution of the lesion he noted<sup>12</sup> that in the chronic stages the alveolar walls and septal interstitial tissues were thickened by a proliferation of fibrous and elastic tissue which was at times extensive enough to restrict the vascular bed and which, in association with arteriosclerosis of the smaller vessels, gave rise to right-sided heart failure in the absence of mitral disease.

(2) *Intraluminal exudate.* Naish first described the hemorrhagic nature of the alveolar exudate. In the early stages of the disease, Paul<sup>23</sup> noted a hemorrhagic and fibrinous exudate which later underwent organization with the formation of casts of loose fibrous tissue within the bronchioles. Edema was often a constituent of the exudate. The presence in the exudate of polymorphonuclear leukocytes in small numbers has been described by many observers.<sup>21, 11, 18</sup> The mononuclear, occasionally multinuclear cells which are most characteristic of the alveolar exudate have been considered phagocytic cells of the reticulo-endothelial system. Gouley<sup>11</sup> described two types of such cells appearing in succession: the foamy endothelial cell present initially was followed by a larger basophilic cell of the "Aschoff" type. The cells which covered the organized exudate within the respiratory bronchioles and alveolar ducts have been designated as alveolar epithelium<sup>18</sup> or as alveolar septal cells.<sup>22</sup> In the "chronic" stages the thickened alveolar walls are lined by cuboidal cells which Gouley<sup>11</sup> considered to be epithelial.

(3) *Hyaline pseudomembrane.* Masson, Riopelle, and Martin<sup>18</sup> described a pseudomembrane which covered the walls of the respiratory bronchioles, obstructing the mouths of, but not actually filling, the alveolar structures. This membrane was thought to be the result of a transformation of fibrinous exudate occurring at the periphery of the lung, where mobility is great, while deeper in the lung, where mobility is less, it became organized by connective tissue, as Paul had described earlier. Hadfield observed that the hyaline fibrinous membrane was similar to that found in many infectious processes (influenza, streptococcal pneumonia, pneumonic plague, etc.) and also in newborn infants whose lungs contained aspirated amniotic fluid. Farber and Wilson<sup>6</sup> demonstrated experimentally that forceful inspiratory effect could produce membranes of similar distribution when there was fluid within the respiratory tree. Hadfield felt that the rheumatic process affected primarily the alveoli and alveolar ducts, resulting in a fibrinous exudate, which was then transformed into a hyaline membrane as a result of dyspnea, probably of cardiac origin.

(4) *Vascular lesions.* In cases of rheumatic carditis, von Glahn and Pappenheimer<sup>29</sup> described changes in the systemic and pulmonary arterioles consisting of fibrin deposition within and about each involved vessel, de-

structive changes and cellular reaction in the vessel wall, and perivascular infiltration by inflammatory cells; these changes later undergo organization. Paul<sup>23</sup> described lesions involving all coats of the arterioles: there were swollen, foamy cells in the intima, pyknotic nuclei in the media, and round cell accumulations in the perivascular zones with thrombi often present in the lumen. In the later stages, there was hyalinization of the intima, scarring of the media, and perivascular fibrosis. Gouley has emphasized the presence of hyaline thrombi in the capillaries of the alveolar walls in the acute stages.

(5) *Aschoff bodies*. Investigators have long searched for Aschoff bodies in the lung. Fraser<sup>8</sup> and Gouley and Eiman<sup>9</sup> reported finding them while others found none.<sup>15, 4, 19, 18, 20, 12, 17, 21</sup>

## II. Clinical

These pathological findings have served as a basis upon which two fairly distinct clinical syndromes have evolved. The first type was described by Rabinowitz<sup>25</sup> in 1926, and, with but minor variations, has been reiterated by many subsequent observers (Howard,<sup>14</sup> Naish,<sup>21</sup> Gouley,<sup>10</sup> and others). In general, the pulmonary symptoms were said to develop insidiously, without upper respiratory infection or chill. Toxicity was not marked and the temperature was reported variously as only slightly elevated,<sup>21, 25</sup> or moderate to high.<sup>10</sup> Gouley felt that the height of the temperature was more a reflection of the severity of the general rheumatic infection than of the pulmonary involvement. The respiratory symptoms were usually slight, consisting of a hacking cough productive of small amounts of sputum which was usually blood-streaked and never purulent.\* Concomitant pleurisy was inconstantly observed. There was no respiratory distress. In contrast to the paucity of pulmonary symptoms, the physical signs were striking and almost diagnostic. Throughout the literature there is a recurring emphasis on the presence of signs of a fleeting pneumonitis: areas of slight dullness, fine râles, and tubular breathing, which tended to be evanescent, reappearing in the same area or in other parts of the lung.<sup>25, 1, 27</sup> The prognosis was apparently unaffected by the pulmonary complication.

Both Hadfield and Gouley separated from the above group a second clinical category—"a small group of patients in whom the pulmonary invasion is extremely rapid and widespread, accompanied by quickly developing dyspnea and cyanosis"<sup>10</sup>—which may terminate fatally. Coburn,<sup>1</sup> Tragerman,<sup>28</sup> Ravenna,<sup>26</sup> and Debré and his co-workers<sup>3</sup> have presented detailed reports on autopsied cases which were characterized clinically by an abrupt onset of profound respiratory distress out of all proportion to the physical findings. In contrast to the severe dyspnea and cyanosis present, physical signs in the chest were completely absent except terminally in many of the reported cases. Pyrexia was moderate to marked, cough was usually

\* Rabinowitz is the only observer who has mentioned the rare occurrence of purulent sputum, but none of his cases was autopsied.



associated with the production of scanty blood-streaked sputum, and heart failure was a variable accompaniment. The outcome was usually fatal in days to weeks. The great similarity between acute pulmonary edema and this form of the disease has led Debré et al. to refer to it as an "acute inflammatory edema of rheumatic origin."

### III. *Roentgenological*

Search of the literature reveals a dearth of descriptions and reproductions of roentgenograms of rheumatic pneumonia. With but one exception, the only illustrations are those of Coburn.<sup>1, 2</sup> Only one of these was from a pathologically proved case; it exhibited a diffuse haze throughout both lungs which seems indistinguishable from the roentgen appearance of pulmonary edema. Poynton and Schlesinger's<sup>24</sup> reproduction, which Gouley considered illustrative of the rapid regression of rheumatic pneumonia, was more likely an instance of massive pericardial effusion with secondary compression atelectasis.

Brief descriptions of the roentgenographic features are furnished by Rabinowitz, Gouley, and Neuburger, Geever and Rutledge. Rabinowitz found that chest roentgenograms were of value only in ruling out bronchopneumonia. Gouley<sup>10</sup> describes roentgen changes consistent with cardiac failure, but ascribes these to rheumatic pneumonia in view of their rapid spread or regression on serial roentgenograms. Corresponding to the migratory nature of the physical signs, Neuburger et al. have also encountered changes resembling "pulmonary congestion" with some frequency, but in one case noted "widely disseminated fine stippling and mottling," which in association with a suitable clinical picture was considered suggestive of rheumatic pneumonia.

In general, despite the non-specific terminology and inadequacy of detail in the descriptions, and the lack of photographic reproductions, these reports suggest that the roentgen features more closely resemble the changes of cardiac failure than those of pneumonia.

### MATERIALS AND CRITERIA

The pathological criteria enumerated above for the diagnosis of rheumatic pneumonia have been employed (figures 1 to 5). A clinical and roentgenological analysis has been made of six cases which at autopsy manifested the characteristic anatomical features of rheumatic pneumonia. In an attempt to evaluate the incidence of rheumatic pneumonia as well as other pleuro-pulmonary complications in chest roentgenograms, a series of 100 episodes of acute rheumatic fever in 91 patients admitted to the New Haven Hospital from 1937 through 1945 has been studied. Three of the six cases verified at autopsy are included in this group; the other three occurred after the close of the period studied. Despite the fact that all of these patients had at least one chest roentgenogram, there was no element of

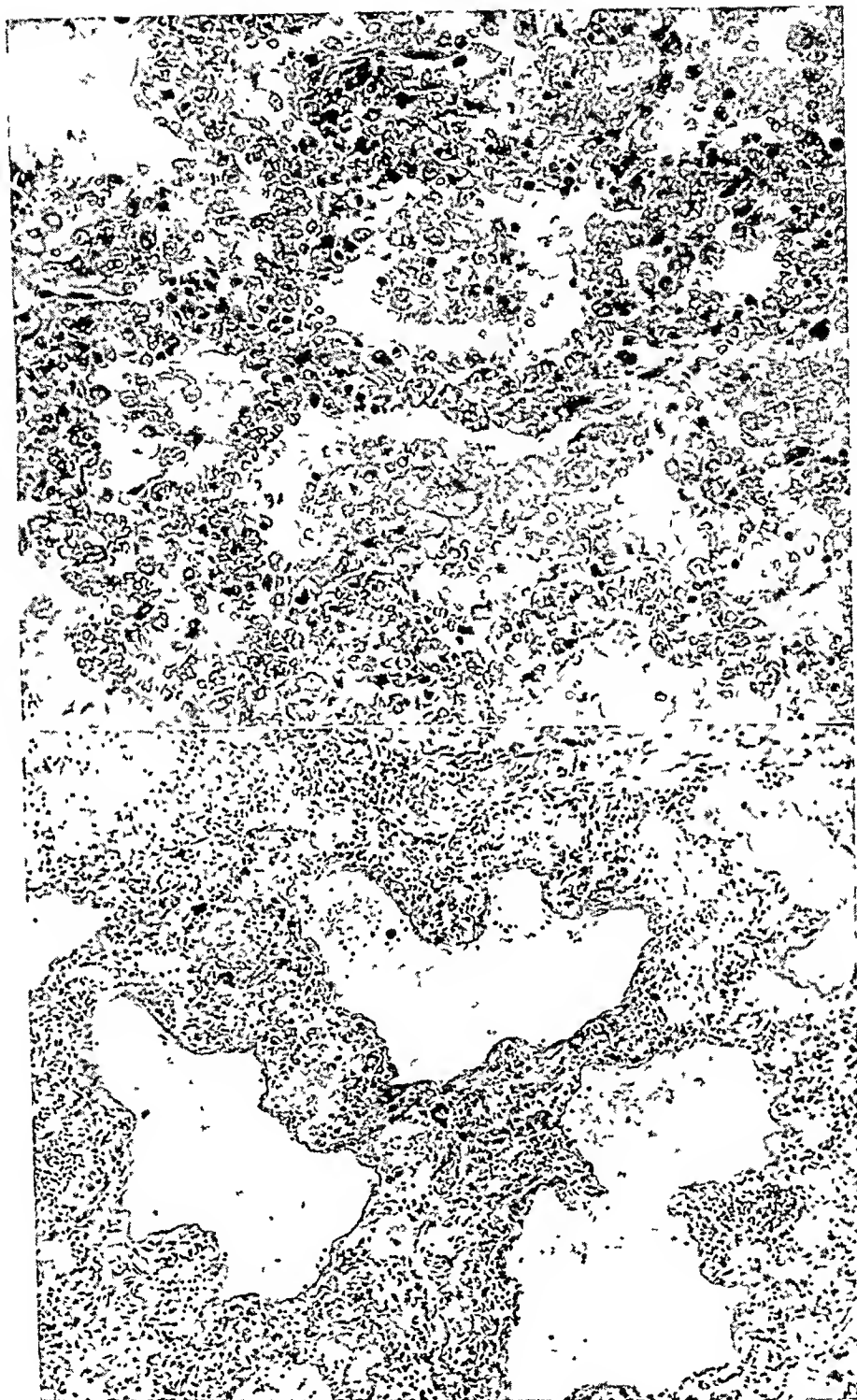


FIG. 1 (above). Case 2. J. P. Alveolar walls thickened by mononuclear cells; capillary congestion; exudate of mononuclear cells and a few red blood cells. Hematoxylin-eosin.  $\times 250$ .

FIG. 2 (below). Case 3. R. M. Respiratory bronchioles and alveolar ducts lined by eosinophilic pseudomembrane that obstructs the mouths of adjacent alveoli; protein precipitate present. Hematoxylin-eosin.  $\times 93$ .

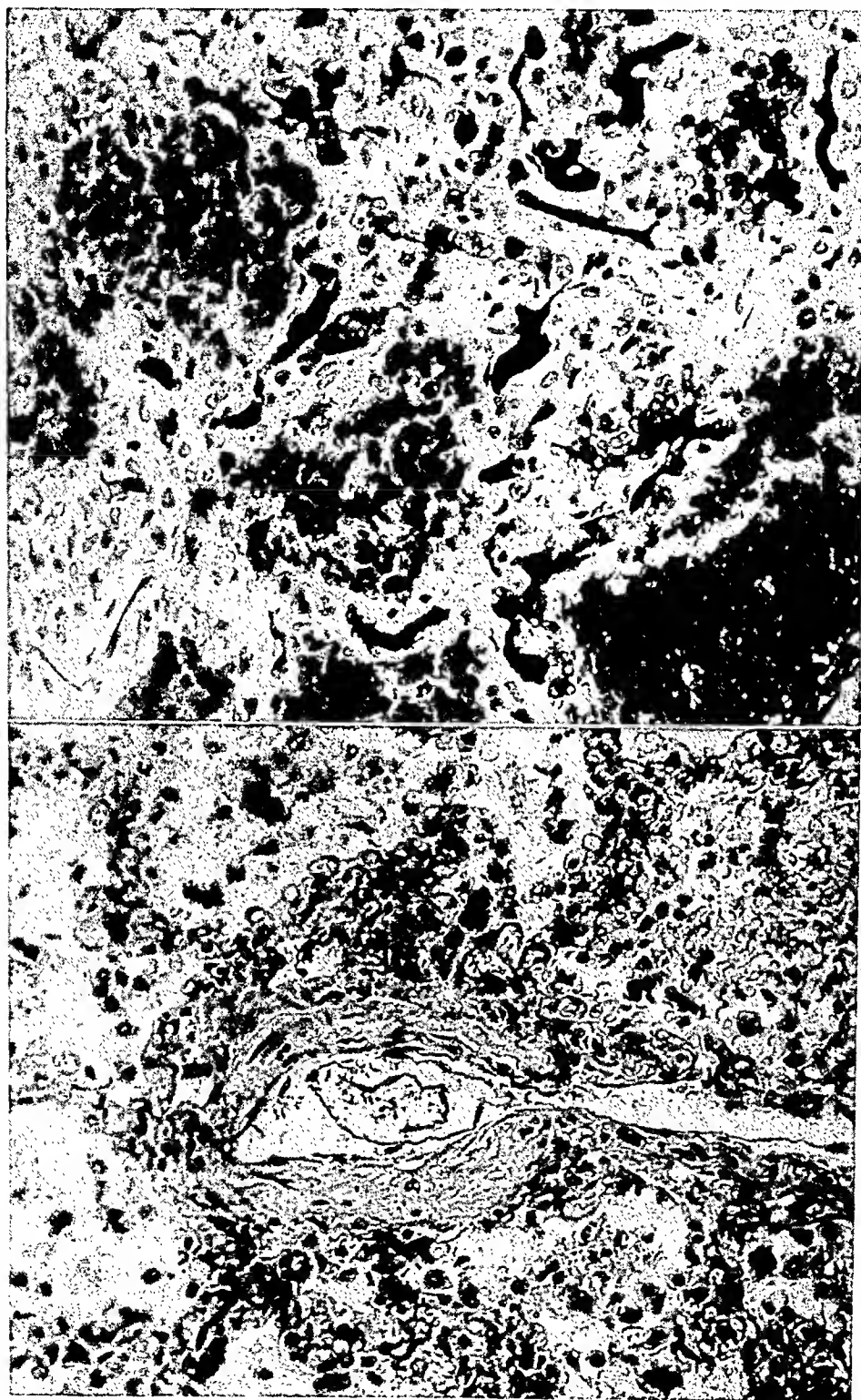


FIG. 3 (above). Case 3. R. M. Hyaline thrombi, appearing black in photograph, in alveolar capillaries; lumen of alveoli filled with red blood cells. Phosphotungstic acid-hematoxylin.  $\times 420$ .

FIG. 4 (below). Case 1. A. G. Small branch of pulmonary artery: hyaline thickening of wall with loss of smooth muscle cells; scattered leukocytic nuclear fragments present. Hematoxylin-eosin.  $\times 300$ .

selection inasmuch as roentgenographic examination is part of the routine investigation of cases of acute rheumatic fever. Throughout this study, the clinical criteria which have been used to establish the diagnosis of acute rheumatic fever were those enumerated by Jones.<sup>15</sup>

#### CASE REPORTS

*Case 1.* A. G., a white female, 23 years of age, was first admitted to the New Haven Hospital on July 16, 1938, with a past history of acute rheumatic fever in 1933, followed by an interval of good health until eight months before admission, when an attack of the "grippe" left in its wake a dry cough. A month before admission the cough became productive of small amounts of blood-streaked white sputum, and the patient was troubled with intermittent left chest pain, probably pleuritic. The sudden onset of severe breathlessness the day before admission led to her hospitalization.

*Physical Examination:* On admission, the temperature was 101°, pulse 132 and respirations 28. The significant findings included the classical signs of mitral stenosis and insufficiency. Some dullness, but very few râles were elicited. The liver was not felt; there was no peripheral edema.

*Course:* Chest films on admission revealed widespread pulmonary infiltration (figure 6), which resolved completely within 10 days (figure 7). Save for the temperature elevation on admission, the patient's three week hospital course was afebrile. The white blood count remained at about 20,000 throughout and repeated throat and blood cultures were negative. Shortly after admission, respiratory symptoms and signs disappeared, and except for the appearance of a migratory arthralgia on July 19, her hospital stay was uneventful, and she was discharged with a diagnosis

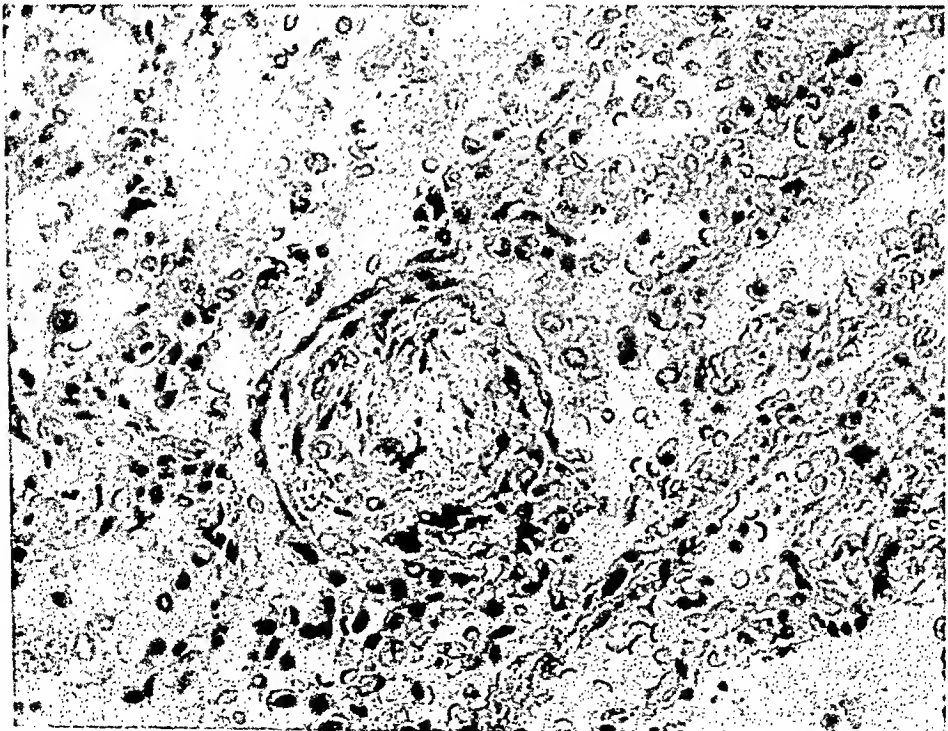


FIG. 5. *Case 2.* J. P. Organization within lumen of alveolus forming connective tissue mass covered by cells resembling epithelium. Hematoxylin-eosin.  $\times 390$ .



of chronic and active rheumatic heart disease, with mitral stenosis and insufficiency, and ? rheumatic pleurisy and pneumonia.

*Interval Note:* Following discharge from the hospital on August 4, 1938, the patient was troubled by intermittent left pleurisy-with fever, cough occasionally productive of blood-streaked sputum, fleeting joint pain, and dyspnea on exertion unrelieved by digitalization.

On Nov. 22, 1939, cough, chest pain, shortness of breath, and orthopnea starting abruptly 20 hours before admission and progressing rapidly to profound dyspnea, led to hospitalization.

*Physical Examination:* On admission, the temperature was 103°, pulse 104, and respirations 44. Patient was dyspneic, orthopneic, and cyanotic. Dullness and many fine and medium moist râles were present at the right base and over the right mid-chest anteriorly. The liver was not felt. There was no peripheral edema.

*Course:* Chest films on admission revealed a multilobar infiltration, more severe on the right (figure 8); repeat films in 10 days again showed complete clearing. On November 23, the day after admission, circulation time was 16 sec. (arm to tongue using 5 c.c. of decholin) and venous pressure was 10.5 cm. (needle 5 cm. below angle of scapula)—findings which were not in keeping with a diagnosis of severe heart failure. The leukocytosis (32,000 on admission) gradually subsided. Within four days the temperature returned toward normal, but a low grade fever and tachycardia persisted throughout. Sulfapyridine was given from November 24 to 28 without apparently influencing the course. Sputum on admission yielded B-hemolytic streptococci on mouse inoculation. Subsequent cultures of the sputum were negative.

The clinical course was attributed to a combination of acute heart failure, active rheumatic fever, and pneumonia.

*Interval Note:* Patient was followed in the Cardiac Clinic. Her course was characterized by periods of dyspnea and tachycardia, interspersed with asymptomatic intervals. On May 23, 1945, the abrupt onset of profound dyspnea, orthopnea, and cough with blood-streaked sputum 48 hours before admission led to her third and last hospitalization. The presence of persistent tachycardia, elevated sedimentation rate, weakness and debility over the preceding winter had led to a diagnosis of subacute rheumatic fever, and one month before admission intermittent right pleural pain appeared.

*Physical Examination:* Patient was desperately dyspneic, orthopneic and cyanotic. Temperature 104.8°, pulse 106, respirations 44. Save for a few rhonchi the chest was clear. The liver was not felt. No peripheral edema.

*Course:* On admission, roentgen-ray examination revealed an extensive pulmonary infiltration throughout both lung fields (figure 9), which remained essentially unchanged on serial reexaminations. Leukocytosis and fever persisted throughout. Throat and sputum cultures were negative. Despite the persistence of marked respiratory distress (necessitating oxygen), no pulmonary physical signs ever developed. The patient died two weeks after admission.

*Necropsy:* There was a hydrothorax of 100 and 150 c.c. on the left and right sides respectively. Dense fibrous adhesions were present at the left base. The heart weighed 320 grams, with hypertrophy of the right ventricle and left auricle, and mitral and aortic stenosis. A few Aschoff bodies were present in the myocardium. The liver weighed 1610 grams and was the seat of marked passive congestion.

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FIG. 6 (above). Case 1. A. G., age 23, female. Patchy areas of finely granular, hazy infiltration, penetrated by coarse linear streaks, are irregularly dispersed throughout both lung fields. This appearance is indistinguishable from pulmonary edema. The heart exhibits a mitral configuration.

FIG. 7 (below). Case 1. Reexamination 10 days later shows complete clearing of both lung fields.





The right lung weighed 1010 grams, the left, 885 grams. The lower lobes were not grossly altered, while the upper lobes were firm, relatively dry, and non-crepitant.

Microscopically there was fairly diffuse thickening of the alveolar walls by large numbers of mononuclear cells, collagen in small amounts, and engorged tortuous capillaries. The alveolar exudate was composed of mononuclear cells (many containing hemosiderin), protein precipitate, fibrin clumps covered by a layer of mononuclear cells, and foci of red blood cells. A small number of alveolar capillaries contained hyaline thrombi; small arterial and arteriolar branches of the pulmonary artery frequently exhibited medial thickening, loss of muscle cells, and leukocytic infiltrations. The inner surfaces of some respiratory bronchioles and alveolar ducts were covered by fibrin, and others by eosinophilic non-fibrinous material (not taking the phosphotungstic acid-hematoxylin stain).

*Case 2.* J. P., a white male, 16 years of age, with a past history of active rheumatic fever in 1935 and 1938, was admitted on December 20, 1943 because of the onset of marked malaise, weakness, dyspnea, and joint pain following a cold two weeks previously.

*Physical Examination:* Patient appeared severely ill, and was dyspneic and orthopneic. Temperature 102°, pulse 120, and respirations 40. The heart was enlarged, rate rapid, signs of mitral stenosis and insufficiency, and possibly aortic insufficiency as well, were present. The chest was clear, save for questionable signs of fluid at the right base. Liver was not felt. No edema.

*Course:* On December 21, 1943, chest films revealed clear lung fields (figure 10), but on December 25, dyspnea and orthopnea became much more severe despite digitalization, and cough productive of blood-streaked white sputum appeared. Signs of fluid at both bases and bilateral moist râles appeared during the subsequent course. On January 4, chest roentgenograms demonstrated an extensive bilateral pulmonary infiltration (figure 11). The white blood count, normal on admission, was elevated from December 28 until death. Fever and tachycardia persisted throughout.

*Necropsy:* There was an ascites of 750 c.c. and a bilateral hydrothorax of 800 c.c. on the right and 400 c.c. on the left. The heart with the adherent pericardium weighed 600 grams; it was hypertrophied and dilated. The chordae of the mitral valve were thickened. There were verrucae on the line of closure of both the mitral and aortic valves. Numerous Aschoff bodies were present in the myocardium. The liver weighed 1,980 grams and exhibited slight evidence of passive congestion.

The lungs weighed 600 grams each and their pleural surfaces were covered by a fibrinous exudate. The cut surface was wet with edema fluid and was variegated in appearance. In focal areas, the alveolar walls were thickened by large numbers of mononuclear cells and a slight increase in collagen. There was an alveolar exudate consisting of large mononuclear phagocytes (at times with foamy cytoplasm), polymorphonuclear leukocytes, red blood cells, protein precipitate, and clumps of fibrin. In a few arterioles the media was thickened and apparently edematous, but no thrombi were seen. The inner surfaces of respiratory bronchioles and alveolar ducts were covered by fibrin strands and also by non-fibrinous material (which neither stained with phosphotungstic acid hematoxylin nor Sudan III). In many foci the exudate within alveoli and respiratory bronchioles was organized to form intraluminal bundles of fibroblasts and collagen, frequently covered by cells resembling epithelium. The interstitial tissues were edematous and also contained foci of fibroblastic proliferation.

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FIG. 8 (above). *Case 1.* Second attack one year later reveals recurrence of the infiltration, which had again completely resolved on reexamination ten days later.

FIG. 9 (below). *Case 1.* Third attack five years later which terminated fatally within 15 days. Serial reexaminations until shortly before death showed no change in the infiltration.



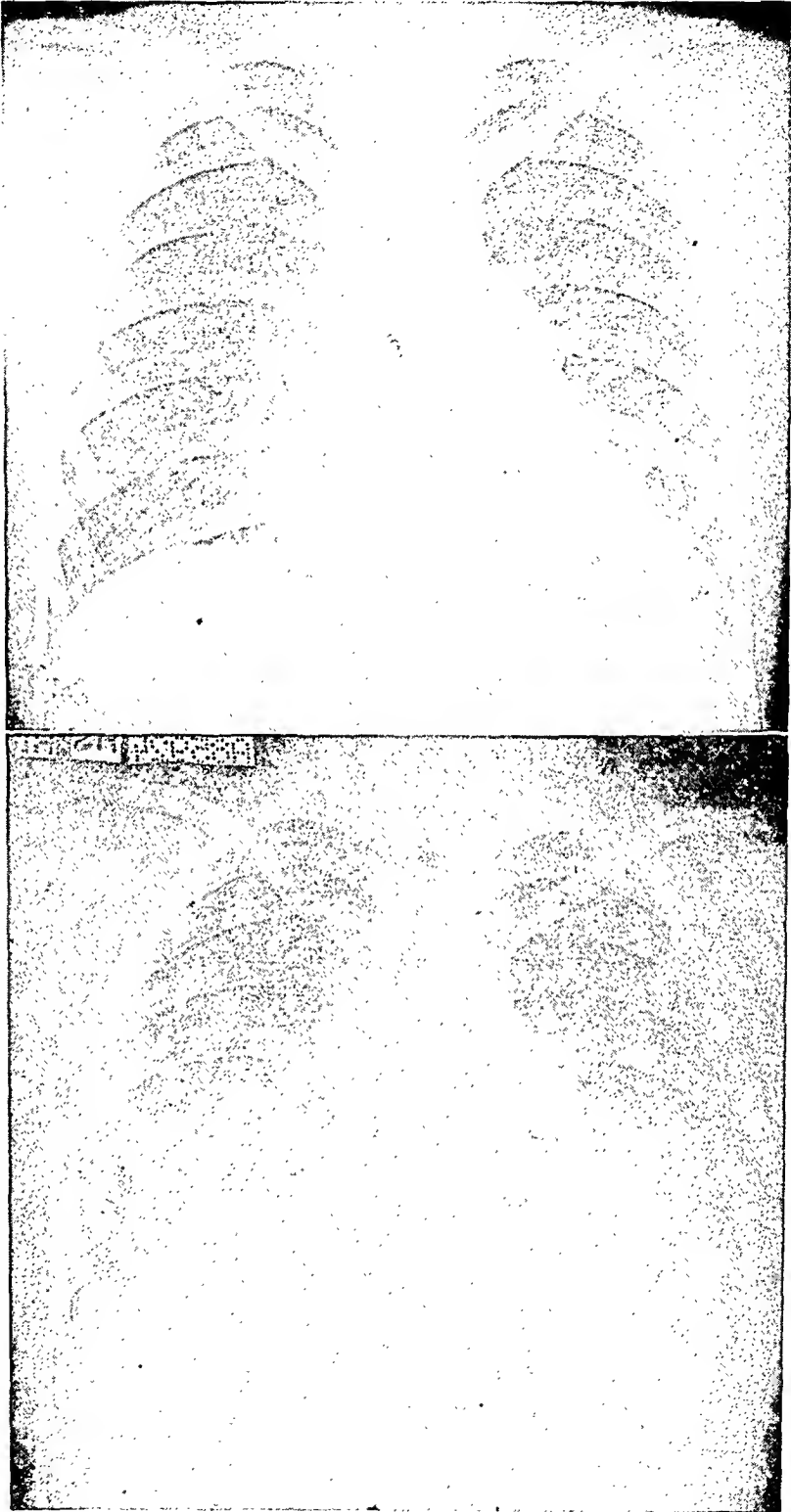


FIG. 10 (above). *Case 2.* J. P., age 16, male. Initial chest film before onset of respiratory distress reveals clear lung fields.

FIG. 11 (below). *Case 2.* Roentgenogram after development of clinical symptoms, showing a mottled and streaked parenchymal infiltration throughout the lower two-thirds of both lung fields, resembling pulmonary congestion.

*Case 3.* R. M., a white female, 13 years of age, was admitted to the New Haven Hospital on January 21, 1940 with a past history of "flu" in March, 1939, followed after seven weeks by a migrating arthritis and chorea. A diagnosis of rheumatic heart disease was made and the patient kept in bed for a total of five weeks. She was asymptomatic until three days before admission, when she developed a sore throat with a temperature of 103° F.

*Physical Examination:* Temperature 102.7°, pulse 30, respirations 20. The significant findings included an enlarged, overactive heart with signs of mitral stenosis and insufficiency, clear lung fields, and no peripheral signs of failure.

*Course:* Temperature and pulse remained elevated and leukocytosis persisted at about 25,000 throughout hospital stay. On the second day, the patient became profoundly dyspneic, with only a few fine râles at both bases, and was unrelieved by subsequent digitalization. Roentgen-ray examination of chest revealed a picture indistinguishable from pulmonary edema (figure 12). Despite constant oxygen, cyanosis became increasingly severe. Death occurred on the sixth hospital day.

*Necropsy:* The heart weighed 330 grams and was dilated as well as hypertrophied. The epicardium was covered by fibrinous exudate. The margins of the mitral and aortic valves were thickened and rolled but not stenotic. These valves and the left auricular endocardium contained verrucae. One chorda of the mitral valve had ruptured. Numerous Aschoff bodies were observed in the myocardium. The liver weighed 1215 grams, and was minimally involved by passive congestion.

The right lung weighed 885 and the left, 710 grams. The surfaces were variegated in color with small red areas on a pale pink-gray background.

Microscopically the alveolar walls were diffusely thickened by mononuclear cells and a few fibroblasts with some increase in collagen. The alveolar exudate consisted of large foamy mononuclear phagocytes, much hemorrhage, scattered polymorphonuclear leukocytes, protein precipitate, and fibrin clumps. Many hyaline thrombi were present in alveolar capillaries and arterioles; in some small arterial branches of the pulmonary artery, the media was thick with loss of smooth muscle cells and scattered nuclear fragments. Some alveolar ducts were lined by fibrin and others by a non-fibrous layer of eosinophilic material (not staining with phosphotungstic acid hematoxylin) which stained faintly with Sudan III. The septal tissues were edematous.

*Case 4.* S. S., a white female, three years of age, was admitted to the New Haven Hospital on February 6, 1946 because of the sudden onset of profound dyspnea and orthopnea, associated with a sore throat, three days before admission. Two days before admission, a dry cough appeared. During the preceding two months, she had suffered recurrent attacks (at least five) of arthritis with fever.

*Physical Examination:* Child was dyspneic, orthopneic, and appeared gravely ill. Temperature 102°, pulse 180, respirations 40. Heart was slightly enlarged, rate rapid with gallop rhythm and a loud systolic murmur at the apex. Lungs clear. Liver was down two fingers'-breadth in the mid-clavicular line. No edema.

*Course:* Roentgen-ray examination of the chest on admission revealed an extensive bilateral pulmonary infiltration (figure 13), which persisted essentially unchanged on serial follow-up examinations until four days before death, when, following a clinical flare-up, it spread to involve both lungs almost completely. Leukocytosis, fever, tachycardia and striking dyspnea persisted throughout. Digitalization was ineffectual. On February 12, a few basilar râles were heard for the first time; by February 16 they had cleared. The liver never increased in size; no peripheral edema appeared.

*Necropsy:* The heart weighed 85 grams and was hypertrophied without significant dilatation. There was no valvular thickening, but verrucae were present along the line of closure of the mitral valve. The myocardium contained a few Aschoff bodies.

The surface of the lungs was light gray-pink, mottled with red-purple areas corresponding to secondary lobules.



FIG. 12 (*above*). *Case 3*. R. M., age 13, female. Large zones of increased density, with irregular margins, occupy the greater part of both lung fields, assuming a "butterfly" distribution and leaving a peripheral clear zone of emphysema. This appearance is identical with that usually designated as pulmonary edema.

FIG. 13 (*below*). *Case 4*. S. S., age 3, female. Note the bilateral, multilobar, linear and reticular infiltration with a peripheral clear zone. Reëxamination one month later, following a clinical exacerbation, showed almost complete obliteration of aerated lung.

The alveolar walls were thickened by mononuclear cells and the alveolar exudate consisted of large mononuclears, phagocytes, focal hemorrhage, and small masses of fibrin frequently covered by flattened cells; there were rare hyaline thrombi in alveolar capillaries. Some respiratory bronchioles were lined by a thin layer of eosinophilic material which at times was sudanophilic; the lumen of others was completely filled by it.

*Case 5.* T. J., a white female, 22 years of age, was admitted to the New Haven Hospital on December 8, 1946. She gave a history of chorea at the age of eleven. She had been well until two days before admission, when she developed profuse sweating, high fever, and embolic phenomena in her extremities.

*Physical Examination:* Patient appeared acutely ill. Temperature 104°, pulse 110, respirations 24. The heart was enlarged, with signs of mitral stenosis, and insufficiency. The lungs were clear. No signs of congestive failure. Several petechiae were present on the sole of the left foot.

*Course:* A heavily positive blood culture for hemolytic *Staphylococcus aureus* led to the administration of penicillin by constant intravenous drip in doses ranging from 1,000,000 to 500,000 units a day until January 10, when the drug was discontinued. Sixteen consecutive blood cultures were negative but four colonies were found on a final blood culture taken three days before death. Two days after admission, venous pressure and circulation time were done because of the presence of dyspnea. The circulation time was normal (17 sec) and the venous pressure was



FIG. 14. Chest roentgenogram of a 53 year old male with arteriosclerotic heart disease, taken shortly before death from congestive heart failure, shows the characteristic features of pulmonary edema. Despite its greater extent, note the striking resemblance of this infiltration to figures 9 and 12.

only slightly elevated (13 cm.). No edema or hepatomegaly was present, but there were a few transient basilar râles. Digitalization was instituted without relief. On January 8 the patient developed a left pleurisy; the temperature, which had hovered around 100 to 101°, rose to 102 to 104°; the white blood count, normal previously, rose to 17,000. Roentgen-ray examination on January 10 revealed a fan-like linear infiltration radiating out from both hilar regions, tending to be lost in a more homogeneous density in the lower lobes—a pattern indistinguishable from cardiac failure. The development of a pneumonia in the face of 500,000 units of penicillin per day, with the peculiar roentgen-ray features mentioned, suggested a non-bacterial etiology. On February 9, patient began to cough up blood-tinged sputum. Reexamination of the chest at that time revealed some increase in the infiltration previously noted. Despite increasing dyspnea, venous pressure and circulation time were normal on February 12. Chest signs were minimal to absent, except terminally.

*Necropsy:* There was a bilateral hydrothorax with 500 and 300 c.c. on the right and left, respectively. The heart was hypertrophied, weighing 310 grams. The mitral valve, which was scarred, contained two friable vegetations, and a similar one was present on the aortic valve; no bacteria were present on culture or microscopic section. Aschoff bodies were numerous in the myocardium. Infarcts were present in the spleen and left kidney. The liver weighed 1,435 grams and exhibited slight passive congestion.

The left lung weighed 710 grams and the right, 740 grams. They were non-crepitant, firm, and mottled dark-red and gray-pink.

The alveolar walls were diffusely thickened by mononuclear cells. The alveolar exudate consisted of large mononuclear cells, scattered polymorphonuclear leukocytes, focal hemorrhage, and protein precipitate. Hyaline thrombi were present in alveolar capillaries and arterioles. Some respiratory bronchioles and alveolar ducts were lined by fibrin, others by a non-fibrinous eosinophilic and sudanophilic substance not stained by phosphotungstic acid hematoxylin; septal edema was present.

It should be noted that there was nothing suggestive of a suppurative process such as would be seen in a staphylococcal pulmonary infection.

*Case 6.* S. deM., a white male, 16 years of age, with a past history of acute rheumatic fever in 1941, was admitted to the New Haven Hospital on December 29, 1945 because of progressive weakness and cough over a period of five weeks.

*Physical Examination:* Patient was dyspneic and orthopneic, and appeared chronically ill. Temperature 103°, pulse 110, respirations 30. The significant findings included an enlarged, overactive heart with signs of mitral stenosis and insufficiency and aortic insufficiency, clear lung fields save for a few moist râles over the left lower lobe, and the absence of peripheral signs of failure.

*Course:* Roentgen-ray examination of the chest on admission revealed clear lung fields; repeat examination on January 30, 1946, following an exacerbation of dyspnea two days previously, showed an accentuation of the vascular structures throughout both lung fields without evidence of intervening parenchymal infiltration. At this time the venous pressure was borderline, and the circulation time slightly elevated; shortly thereafter, peripheral edema appeared. Digitalization afforded no relief. Tachycardia and dyspnea became increasingly severe and the production of blood-streaked sputum, noted on admission, recurred. Physical signs in the chest were slight until shortly before death. Patient died on February 11, 1946, about one and one-half months after admission.

*Necropsy:* There was subcutaneous edema of the legs, sacrum, and face. The heart, weighing 600 grams, was hypertrophied and dilated. The mitral and aortic valves were thickened, but not stenotic, and contained verrucae on the line of closure. There were many Aschoff bodies in the myocardium. The liver weighed 1435 grams and showed passive congestion.

The right lung weighed 1200 grams and the left 800 grams. There were small infarcts in the anterior margins of the right upper and left lower lobes, with a fibrinous pleural exudate overlying and surrounding each. The surface was mottled, light pink and dark red.

In focal areas the alveolar walls were thickened by increased numbers of mononuclear cells and fibroblasts. The alveolar exudate consisted of mononuclear phagocytes, foci of hemorrhage, precipitated protein, and fibrin strands. A few hyaline thrombi were present in the alveolar capillaries and arterioles, and there was loss of smooth muscle cells with scattered nuclear fragments in the walls of arteries; some respiratory bronchioles were lined by fibrin, others by a non-fibrinous eosinophilic and sudanophilic membrane not stained by phosphotungstic acid hematoxylin. The intra-luminal exudate in alveoli and respiratory bronchioles was organized by tuft-like masses of fibroblasts and collagen, covered by flattened epithelial-like cells; there was also interstitial fibroblastic organization.

### CLINICAL AND ROENTGENOLOGIC FEATURES

The principal findings in the six verified examples of rheumatic pneumonia are summarized in tables 1 and 2. All cases exhibited clinical, laboratory, and anatomical evidence of active rheumatic carditis. In contrast to the experience of Masson et al.<sup>18</sup> five of the cases were beyond the

TABLE I  
Summarized History of Cases of Rheumatic Pneumonia

Name <sup>1</sup>	Age	Sex	Prev. Attacks of Active R.F.	Onset of R.F. to Onset of Pneum.	Rapidity of Onset	Chill	Hacking Cough	Dyspnea	Pleurisy
A. G. <sup>c</sup>	29	F	3	3½ mos.	xxxx	0	x	xxxx	x
J. P.	16	M	2	16 days	xxxx	0	x	xxxx	x
R. M. <sup>2</sup>	13	F	1	4 days	xx	0	x	xxx	0
S. S.	3	F	0	2 mos.	xxxx	0	x	xxxx	0
T. J.	22	F	1	1 mo.	xxx	x <sup>3</sup>	x	xx-xxxx	x
S. deM.	16	M	1	10 weeks	xxx	0	x	xxx	0
A. G. <sup>a</sup>	23	F	1	8 mos.	xxx	0	x	xxx	x
A. G. <sup>b</sup>	25	F	2	12 mos.	xxx	0	x	xxxx	0

<sup>a, b, c</sup> Represents three attacks of rheumatic pneumonia in one patient.

<sup>1</sup> All cases had active carditis and were in cardiac failure.

<sup>2</sup> Only case with pericarditis.

<sup>3</sup> Had staphylococcal endocarditis and septicemia.

first decade of life and two were in the third decade. Two of the six cases were males. Five had had previous attacks of active rheumatic fever. In one case (A. G.), three recurrent attacks of rheumatic pneumonia, the last terminating fatally, punctuated a low-grade subacute rheumatic fever. Pericarditis occurred in only one (R. M.) The pneumonic manifestations may develop almost simultaneously with the onset of a fulminating, acute rheumatic fever (R. M.), or light up a smouldering subacute rheumatic fever that has gone on for weeks or months.

*Mode of Onset:* A striking feature has been the abrupt onset, in the space of hours, of profound respiratory distress.

TABLE II  
Summarized Findings and Course of Cases of Rheumatic Pneumonia

Name	Temperature		Sputum Amt.	Type <sup>1</sup>	Phys. Signs	No. of Lobes Involved	White Bl. Count		Sputum, Throat Cultures	Course	Result
	Adm.	Later					Total	% Pmn's			
A. G. <sup>c</sup>	104.8	101-2	x	MB	0-x	5	22.0	80-90	0	15d	D
J. P.	102	102-3	x	MB	xxx	4	16.0	78	0	12d	D
R. M.	102.7	102-3	0	0	x	5	25.0	85	0	5d	D
S. S.	102	100-102	0	0	0-x	5	14.5	80	0	31d	D
<sup>3</sup> T. J.	105	100-102	x	MB	0-x	5	5.0-18	90	x	40d	D
S. deM.	101	98-100	x	MB <sup>1</sup>	x-xx	5	9.0	75	0	12d	D
A. G. <sup>a</sup>	101.4	98.6	x	MB	x	3-5	18.0	75	0	8d	L
<sup>2</sup> A. G. <sup>b</sup>	103	101-98.6	x	MB	xx	5	26.0	93	x	7d	L

<sup>a, b, c</sup> Represents three attacks in one patient.

<sup>1</sup> M mucoid.

B blood streaked.

B<sup>1</sup> diffusely bloody.

<sup>2</sup> No response to sulfapyridine.

<sup>3</sup> Patient had acute staphylococcal endocarditis; septicemia, but not pneumonia responded to penicillin.

*Dyspnea, Orthopnea, and Cyanosis:* This triad was a constant manifestation of the disease, far overshadowing all other symptoms. Respirations were rapid and moderately deep, and all patients required oxygen.

*Cough and Sputum:* A dry, hacking cough, occasionally productive of small amounts of white, mucoid sputum which was usually streaked with blood was present in all cases. At times the sputum became grossly bloody, but the "rusty" sputum of pneumococcal pneumonia was never seen. In no case was purulent sputum observed.

*Pleurisy:* Pleuritic pain of fleeting nature was inconstantly present. It occurred either as a prodromal manifestation or appeared during the course of the disease, but in no instance was it a dramatic initial symptom as in lobar pneumonia.

*Fever:* The temperature was moderately to markedly elevated, ranging from 100° to 105° F. Whether this is a reflection of the severity of the systemic rheumatic infection, as Gouley maintains, or is directly attributable to the pulmonary complication, is not clear.

*Physical Signs:* In contrast to the striking air hunger, the physical signs in the lung were surprisingly few. In one case (A. G.<sup>c</sup>) the lungs were completely clear to physical examination throughout the course despite roentgen evidence of a diffuse infiltration involving all five lobes. Another case (S. S.) with profound dyspnea and roentgen evidence of equally extensive infiltration was similarly devoid of physical signs except for transient fine basilar râles about one week after admission and again terminally. This dichotomy between the paucity of physical signs and the profundity of respiratory distress was noted to a variable extent in all cases. In only one case (J. P.) were physical signs in the chest considered prominent, and at autopsy a large bilateral pleural effusion was found.

*Cardiac Failure:* Despite the fact that some degree of cardiac failure was present in all cases, there were few physical signs in the lung which were attributable to it. The possibility that pulmonary signs of decompensation might mask the otherwise "silent" character of the pneumonic process must, however, be kept in mind. There was failure to respond to digitalis in every case, as might well be expected in the presence of active carditis.

*Laboratory Data:* The *white blood cell count* was elevated in all cases ranging from 14 to 26 thousand. *Differential counts* revealed a polymorphonuclear leukocytosis of from 75 per cent to 93 per cent of the total count. There was no anemia except in the case (T. J.) with a complicating staphylococcal septicemia.

Despite the presence of active rheumatic fever throughout the series, only one sputum culture was positive for  $\beta$ -hemolytic streptococci, although both sputum and throat cultures were repeatedly taken. No pathogenic pneumococci (by mouse inoculation and typing) were found.

*Roentgen Findings:* The roentgen appearance of rheumatic pneumonia is indistinguishable from that usually associated with cardiac failure. The significance of the pulmonary roentgen findings in rheumatic heart disease with and without decompensation has yet to be elucidated. Hence, differentiation between changes ascribable to such an inflammatory process and those secondary to purely cardiodynamic factors, on the basis of roentgen-ray features alone, is impossible. For convenience, the pulmonary roentgen changes associated with rheumatic heart disease will be grouped under three categories: \*

(1) *Vascular engorgement:* by this term is meant an increased prominence of the pulmonary arterial shadows throughout both lung fields. The precise relationship of this finding to cardiac failure is obscure.

(2) *Pulmonary congestion:* by this term is meant a roentgen appearance characterized by the presence of coarse, fuzzy, arborizing linear shadows, radiating out from the hilar regions and presumably vascular, whose irregular margins merge gradually with the adjacent aerated lung parenchyma. Although such an appearance in itself is nonspecific, in association with cardiac enlargement and/or suitable clinical data it is usually attributable to cardiac failure.

(3) *Pulmonary edema:* by this term is meant a roentgenographic appearance characterized by a diffuse, moderately dense, fluffy or hazy parenchymal infiltration which is usually bilateral, multilobar, and often assumes a "butterfly" distribution, with a peripheral clear zone of emphysema, and with varying degrees of obliteration of individual vascular shadows. Cardiac failure is usually present with this condition but is probably not causally related to it. Luisada<sup>17</sup> has summarized the evidence for this view.

It should be recognized that these terms, as used here, refer only to ob-

\* This classification should not be construed as all-inclusive since other pulmonary changes occur in association with rheumatic fever which are not subsumed under any of these categories.



jective roentgen findings and do not imply cardiac failure as a causal factor. This point deserves emphasis inasmuch as identical roentgen changes have been present in pathologically verified cases of rheumatic pneumonia.

The cases studied exhibited each of the three appearances described above, though pulmonary edema was the most common. In the presence of suitable clinical data, a roentgen appearance characterized by widespread, bilateral, multilobar, non-segmental infiltration should suggest the diagnosis of rheumatic pneumonia and aid in its differentiation from bacterial and primary atypical pneumonic consolidations.

*Course and Prognosis:* In view of the fatal outcome of all cases in this series, the disease appears to have a grave prognostic significance. Death occurred within 5 to 40 days of the onset of this complication. It should be noted, however, that one case (A. G.) survived two probable attacks before succumbing to the third. In these two non-fatal attacks, roentgen-ray evidence of complete resolution was present within 10 days, although it may have occurred sooner.

*Response to Treatment:* Salicylates did not alter the course of the disease. Penicillin, administered as a constant intravenous drip of 500,000 to 1,000,000 units per day over a period of several weeks, did not prevent its development in one case (T. J.). In one of the non-fatal attacks (A. G.<sup>b</sup>), resolution did not appear causally related to the administration of sulfa-pyridine.

*Differential Diagnosis:* There is little difficulty in distinguishing rheumatic pneumonia, in the form here encountered, from bacterial or primary atypical pneumonias. The mode of onset, character of the sputum, paucity of physical signs, and absence of pathogenic organisms in the sputum, together with roentgen findings of a diffuse, bilateral, non-segmental infiltration, all combine to exclude a diagnosis of bacterial or primary atypical pneumonia.

It is apparent that the main problem consists in distinguishing rheumatic pneumonia from various stages of cardiac failure. This is impossible by roentgen-ray examination alone. Certain clinical features, however, aid in making a differential diagnosis. On the basis of the cases reported here and those described in the literature, the absence of an active carditis makes the diagnosis of rheumatic pneumonia untenable. Where cardiac decompensation is not present, as reported by Coburn, the roentgen-ray features assume added significance. In the presence of a widespread pulmonary infiltration, associated pleural pain would suggest an inflammatory rather than a purely congestive origin. An abrupt onset of profound dyspnea without commensurate physical signs would also favor the diagnosis of rheumatic pneumonia. The principal differential features are summarized in table 3.

*Roentgen Incidence of Pulmonary Complications of Acute Rheumatic Fever:* In an attempt to evaluate the roentgenographic incidence and nature of pleuro-pulmonary complications of active rheumatic fever a series of 100

TABLE III  
Differential Diagnosis

	Acute Pul. Edema	Rheum. Pneumonia	Bact. Pneumonia
Presence of active carditis	Not necessarily	Always	Rare
Fever	Normal-mod.	High	High
Pleuritic pain	Absent	Frequent	Frequent
Dyspnea	Profound	Profound	Commensurate with physical signs
Sputum	Pink, frothy	Mucoid, blood-streaked	Purulent
Physical findings	Marked	Few	Moderate to marked
X-Ray			
Distrib.	Non-segmental	Non-segmental	Segmental or lobar
No. lobes	Multiple, bilateral	Multiple, bilateral	Rarely more than 2 or 3 lobes
Type of lesion	Soft, hazy, patchy infiltration	Soft, hazy, patchy infiltration, or linear and reticular radiation from hilar regions	Dense, homogeneous consolidation
Pathogens in sputum	None	Usually absent	Present

admissions of 91 patients with active rheumatic fever was studied. The results of this study are presented in table 4. Bacterial pneumonia appears to be a rare complication of active rheumatic fever, since it occurred in only two of 100 attacks in the present series; both of these were cases of pneumonitis on a bronchiectatic basis, and no instance of lobar or primary atypical pneumonia was encountered. Such a low statistical incidence of intercurrent pneumonias facilitates the differential diagnosis of rheumatic pneumonia.

TABLE IV  
Roentgen-Ray Findings in Clinical Types of Rheumatic Fever—100 Attacks in 91 Cases

	Arthritis Alone, 13 Attacks	Carditis without Decompensation, 66 Attacks	Carditis with Decompensation, 21 Attacks
Vasc. Engorgement and Pulm. Congestion	0	6	21 <sup>a</sup>
Pleural Effusion	0	9 <sup>b</sup>	7 <sup>c</sup>
Atelectasis	0	3	1
Bact. Pneumonia	0	2	0
Pulm. Infarct	0	0	2
Rheum. Pneumonia	0	0	6
Totals	0	20	37

<sup>a</sup> In two cases engorgement was questionable as vessels were obscured by rheumatic pneumonia.

<sup>b</sup> Eight patients had pleuritic pain.

<sup>c</sup> Four patients had pleuritic pain.

The most common pulmonary lesions noted, occurring in 27 per cent of the attacks, were vascular engorgement and pulmonary congestion usually associated with cardiac failure. In a few instances, infiltrations resembling vascular engorgement were not accompanied by clinical evidence of cardiac decompensation. The possibility that these infiltrations represented mild,

non-fatal instances of rheumatic pneumonia was considered, but their symptomatology was not that of the proved cases. In the hospital material studied, the incidence of rheumatic pneumonia was 5 per cent.

### DISCUSSION

It is difficult to resolve the discrepancy between the grave clinical picture encountered in these cases (and in those reported by Ravenna, Coburn, and Debré et al.), and the milder syndrome described by Rabinowitz and others. Inasmuch as the two groups were morphologically identical at autopsy, the latter form of the lesion cannot be dismissed as representing an erroneous diagnosis. Despite careful search, however, no instances of "fleeting pneumonitis" compatible with the published descriptions of this mild variant were encountered in the hospitalized cases studied. Inasmuch as the clinical and roentgenological criteria for the diagnosis of rheumatic pneumonia are still inconclusive, the necessity for postmortem verification introduces a possible error in the evaluation of the course and prognosis of the disease by excluding mild cases. Accordingly, the clinical and roentgenological features which are observed in fatal cases need not be expected in more benign instances. The clinical nature of such mild episodes must await the opportunity to observe and study adequate numbers of them in which autopsy verification is possible owing to death from accidental or unrelated causes.

It is probable that gradations in the pathological extent and severity of the disease would be reflected in the prognosis and clinical syndrome. However, any simple and direct correlation between individual clinical symptoms and the anatomical lesions is only speculative at this time. In contrast to the lungs of acute pulmonary edema, the sectional pulmonary surfaces in rheumatic pneumonia, though appearing moist, fail to exude frothy, serosanguinous fluid. This absence of a thin, liquid exudate may explain the striking absence of râles in the latter condition, while the peripheral zone of emphysema so clearly brought out by roentgen examination may be related to the absence of dullness to percussion or changes in tactile fremitus. The profound dyspnea which characterized the severe cases encountered in the study can be considered either a cause (as Farber and Wilson have indicated) or an effect of the deposition of hyaline pseudomembranes in the terminal bronchioles and alveolar ducts, with consequent atelectasis of multiple tributary alveoli. Epstein and Greenspan have suggested that dyspnea due to associated cardiac decompensation is necessary for the conversion of the intraluminal exudate into these hyaline pseudomembranes. On this basis, however, cardiac failure becomes an integral and necessary component of the disease. Such a conclusion is at variance with Coburn's observation of a verified case in which no evidence of decompensation was present, and with the minimal degrees of decompensation in two of the six cases reported here. There can be no doubt that an active rheumatic carditis with at least some degree of failure is almost always associated with

rheumatic pneumonia, but the available evidence does not permit any conclusions concerning the causal relationship between the two conditions.

Despite their distinctly different pathologic character, pulmonary edema and rheumatic pneumonia share a common, or at least closely similar, roentgen appearance. This fact, together with the non-segmental, multilobar distribution, suggests that the pathogenesis of rheumatic pneumonia is based upon a diffuse pulmonary vascular lesion, to which the exudate, pseudo-membranes, and cellular infiltration are secondary. This inference is supported by the histological studies of cases of varied duration reported by Epstein and Greenspan and by Gouley. It is possible that further evidence concerning the evolution of the disease will result from careful study of serial chest roentgenograms in patients with severe acute rheumatic fever.

### SUMMARY AND CONCLUSIONS

1. Six cases of active rheumatic fever with carditis, presenting the characteristic pathological features of rheumatic pneumonia, have been studied. A uniform clinical picture was encountered, characterized by an abrupt onset of profound respiratory distress in the absence of commensurate physical signs in the chest. Hacking cough with scanty, blood-streaked sputum, moderate to high fever, and leukocytosis were also present. The disease was manifested roentgenologically by a bilateral, multilobar, non-segmental infiltration which resembles pulmonary edema.

2. The clinical and roentgenological features of rheumatic pneumonia were observed in five of 100 attacks of active rheumatic fever occurring in 91 patients. No instance of lobar or primary atypical pneumonia was encountered in this series, and pneumonitis secondary to bronchiectasis was found only twice. Rheumatic pneumonias therefore appear to be more frequent than intercurrent pneumonias during the course of active rheumatic fever.

3. All cases of rheumatic pneumonia observed in this study terminated fatally. Therefore, this manifestation of rheumatic fever would appear to carry a grave prognostic significance.

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## BRONCHIAL SPASM IN CARDIAC ASTHMA \*

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THE object of the experiments to be reported here was to elucidate some of the problems associated with the dyspnea of heart disease. Specifically, we wanted to learn something of the mechanism of the wheezing sometimes found in heart disease, to study the vital capacity in this type of heart failure and in that associated with basal râles, to study the effect of venesection on the vital capacity in such cases and to study as far as possible the expiration time and the velocity of expiration in heart disease.

The fact that cardiac asthma may simulate bronchial asthma closely has of course been known by clinicians for hundreds of years. Until quite recently the examining physician had consciously or unconsciously, when confronted with wheezing respiration, used the presence or absence of moist râles at the bases of the lungs as an important criterion for the differential diagnosis. In other words, if he heard sibilant râles scattered throughout both lungs with moist râles at one or both bases, he classified the case as one of cardiac asthma. However, if he heard wheezing râles diffusely scattered throughout the chest without basal râles, he usually made the diagnosis of bronchial or allergic asthma.

In 1939, studies from this department<sup>1</sup> showed that this concept was erroneous for several reasons. Most important of all, it was demonstrated at that time that wheezing might occur in cardiac asthma without the presence of basal râles and that this wheezing was entirely indistinguishable from the point of view of physical signs from the râles of bronchial asthma. Furthermore, it was shown that some cases of true allergic asthma were complicated by moist râles at the bases. We also showed by means of studies of the velocity of the circulation that estimation of the circulation time could be used to distinguish, in the great majority of cases, cardiac from bronchial asthma.

Soon thereafter it was found that the then currently held idea that cardiac and bronchial asthma could be differentiated from each other by the response to adrenalin was mistaken. Most cases of cardiac asthma, especially if they were of the type that had wheezing respirations, a type which we designated as "asthmatoïd heart failure," were relieved promptly by the administration of adrenalin. We felt therefore that if the mechanism of the dyspnea and its relief by adrenalin were better understood, much light could be thrown on the entire subject of the differential diagnosis. It was with this in mind that the present study was undertaken.

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It is not difficult for most of us to understand the reasons for the decrease in vital capacity when moist râles are present in the lung bases. As shown diagrammatically in figure 1, No. 2, free edema-fluid is present in the alveolar spaces. Basal râles are heard in such cases and if there is enough fluid to rattle around in the bronchi, the familiar signs of pulmonary edema are

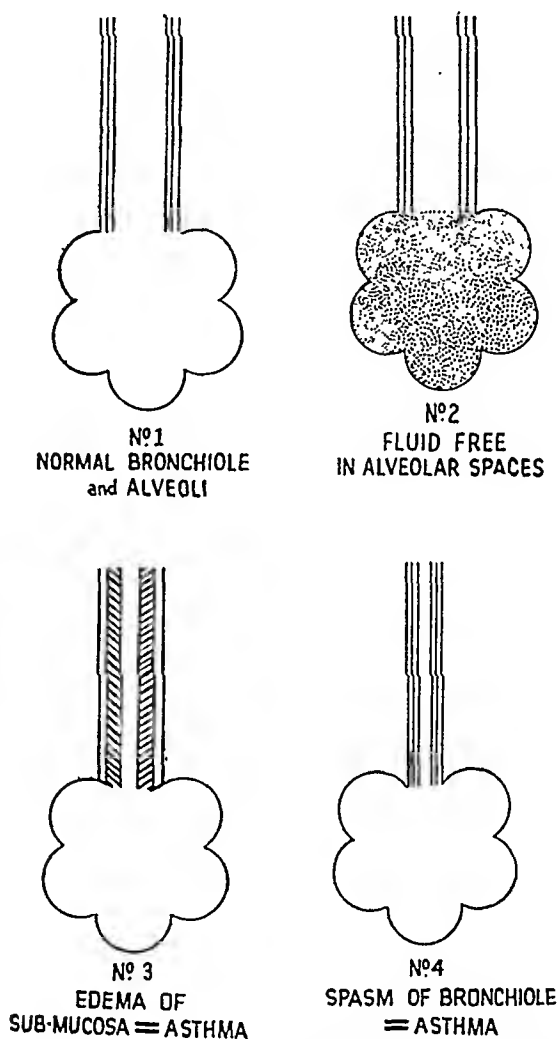


FIG. 1. Diagrams to illustrate genesis of cardiac asthma.

heard. It is somewhat more difficult to understand how heart failure leads to wheezing respirations without moist râles. A possible mechanism, analogous to that occurring in bronchial asthma, is shown in figure 1, No. 3 which schematically shows encroachment on the lumen of the smaller bronchioles by severe edema and engorgement of the submucosa. At the time that our first paper on asthmatoïd heart failure was published, we thought that this was probably the dominant mechanism. Since then, however, we have given a great deal of thought to the possibility that bronchial spasm, on a reflex basis, might be the principal factor (figure 1, No. 4).

Patients with heart failure were studied in several groups in the wards of the Kings County Hospital, the Goldwater Memorial Hospital and in the

cardiac station of the Bushwick Hospital. The first group was constituted of cases with sibilant râles alone but no evidence of basal râles (table 1). There were nine such cases all of which had heart failure as evidenced by other physical signs and especially by a marked prolongation of the circulation time. There was only one case of rheumatic heart disease, five cases of hypertensive heart disease and three with coronary heart disease and myofibrosis cordis. Vital capacity studies were done with these patients in as nearly basal conditions as possible. Two tests were taken not less than

TABLE I  
Heart Disease: "Asthma": No Basal Râles

Age	Vital Capacity	Increase After Adrenalin
51	2.1	450
52	2.4	510
61	1.6	400
45	1.9	325
23	2.3	520
49	2.7	400
55	1.2	225
56	2.3	425
56	1.9	470
Average 49	Average 2.15	Average 425

five minutes apart and, as is usual in such cases, the second test almost invariably gave the higher figure. In each case the expiration time was noted and the expiration velocity in terms of c.c. per second was charted. The vital capacity in each case was found to be sharply reduced below the calculated normal estimated by the method of Edward and Wilson. The expiration time was the same as that found in normal individuals but the expiration velocity was also markedly decreased.

One-half c.c. of adrenalin was injected subcutaneously in each of these patients and vital capacity studies were taken anywhere from 30 to 90 seconds later and four to five minutes after that. In each case there was a sharp increase in the vital capacity over the reading previously obtained. This increase averaged about 510 c.c.. In five cases inhalations of vaponephrin were used and the results were entirely comparable, an increase in vital capacity taking place almost immediately. The patients almost all felt much improved and no untoward effects were noted although the experiments were started with misgivings.

A control group was used, of 11 cases (table 2), in whom there was marked cardiac failure with basal râles but without wheezing. The vital capacity was even lower than in the previous group, a finding which was not surprising in view of the fact that these cases almost all represented a more advanced stage of failure. Adrenalin or vaponephrin was administered to each of these patients with little or no increase in the vital capacity. Seven patients showed increases of less than 50 c.c. and four patients showed increases of less than 100. In no case was there an increase of more than 100 c.c.



TABLE II  
Heart Failure: No Wheezing: Basal Râles

Age	Vital Capacity	Increase After Adrenalin
50	1.4	75
22	2.0	120
61	1.6	50
49	1.5	50
72	1.3	75
71	0.9	105
45	2.1	75
51	1.4	0
62	1.7	25
60	1.2	100
43	1.3	55
Average 53	Average 1.4	Average 59

Four of the patients from the first group were observed several months later at which time they had passed into the second group. These were patients that had started with asthmatic breathing entirely resembling that of bronchial asthma, a stage followed several months later by frank cardiac failure in which numerous râles were heard at both bases. In these cases, a further reduction in the vital capacity was noted to have occurred as the disease progressed and there was little or no response to the administration of adrenalin.

Five normal individuals were used as controls. These were patients with no cardiac or pulmonary disease in whom the vital capacity was 4.5 liters or over. The administration of adrenalin produced no change in the vital capacity.

Several other measurements were taken on the same patients. The expiratory time was taken in most of the subjects. This is the minimum duration of the maximum expiration. The subject is told to exhale as rapidly as possible after completing his deep inspiration and the time is carefully clocked. The expiratory velocity was estimated in terms of c.c. per second. A third measurement, the expiratory pressure, in terms of millimeters of mercury was measured in most of the subjects. The cuff connection of a mercury sphygmomanometer was attached to a rubber tube 50 centimeters long identical with that used in the spirometer. The subject inhaled as deeply as possible and then exhaled forcibly into the manometer in about the same way as for the vital capacity test.

Our results were in agreement with those reported by Desiderio Gross<sup>2</sup> in 1943 with respect to normal individuals. The expiratory time averaged 3.5 seconds and the expiratory velocity about 1360 c.c. per second. The expiratory pressure averaged 122 millimeters of mercury. All of these figures are in close agreement with those obtained by Gross. However, the expiratory time was found to be prolonged in all patients suffering from dyspnea, with or without wheezing respirations. All had expiratory times of 4.0 seconds or higher. Naturally the expiratory velocity was considerably decreased in all cases. Gross, on the other hand, found that the

expiratory time was normal in patients with decompensated heart disease. The expiratory pressure we found, as did Gross, to be markedly decreased in all cases of heart failure with pulmonary symptoms. It was less than half that of normal individuals and averaged 63 millimeters of mercury.

Observations were also made on the effects of phlebotomy on the vital capacity of both normal and cardiac subjects. These results will be reported elsewhere. Suffice it to say that our results merely confirmed the observations of Budelmann<sup>3</sup> that the vital capacity is increased by venesection in patients with cardiac failure and those of Glaser and Macmichael<sup>4</sup> that a similar increase is found in normal individuals.

Several explanations of the increase in vital capacity after adrenalin in our subjects with wheezing respiration are possible and I do not see how, in the light of the information available at present, one can make a final decision. It is possible, of course, that the adrenalin may act by increasing the efficiency of heart action or by decreasing submucosal edema or by relieving congestion in the inter-alveolar framework. I am not inclined to believe that any of these explanations is correct. It seems to me that the speed with which the reactions took place, namely, as rapidly as they could be measured, i.e., within 30 seconds, and the extent of the increase in vital capacity, that relief of spasm of the smaller bronchioles is the most likely explanation.

#### SUMMARY

1. Bronchial spasm is an important element in certain types of heart failure.

2. Cardiac asthma may occur with asthmatic wheezing and without basal râles. Such cases are indistinguishable by means of physical signs from bronchial allergic asthma and may, as in the case of the latter, be improved by the use of adrenalin.

3. In normal individuals, the administration of adrenalin does not increase the vital capacity.

4. In patients with cardiac failure without basal râles but with wheezing respiration, the administration of adrenalin increases the vital capacity sharply.

5. The vital capacity is not increased by adrenalin in patients with basal râles.

6. The expiratory pressure is sharply decreased in patients with pulmonary congestion or wheezing respiration and the expiratory time is prolonged.

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# THE USE OF METHYL-ISO-OCTENYLAMINE IN MIGRAINE\*

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THE mechanism by which headache is produced in the migrainous patient is not entirely understood but it almost certainly is a vascular phenomenon dependent upon alterations in caliber of the cerebral, dural, or scalp vessels. Those drugs which most commonly relieve the pain are sympathicomimetic and vasoconstrictor in their action. Of these the one which has best stood the test of time is ergotamine tartrate (Gynergen, Sandoz), but there are certain disadvantages to the use of this material. Aside from dangers of ergotism from prolonged administration, there are frequently unpleasant symptoms such as nausea, vomiting, paresthesias in the hands, and sensitivity to temperature change. In addition migraine headache tends to occur most frequently just before the onset of the menstrual flow and the administration of ergot at that time is frequently accompanied by distressing dysmenorrhea. Many of these unpleasant side effects are less common when the newer ergot derivative, D. H. E. 45 (Dihydroergotamine, Sandoz), is used. Generally speaking, this material, the use of which was first described by Horton,<sup>1</sup> is probably the most universally satisfactory agent for the relief of migraine headache now available.

However, in a desire to avoid the use of ergot in any form in patients who suffer from frequent episodes of migraine headache, other drugs having a similar action have been studied. Of these, methyl-iso-octenylamine † has proved most useful. This material was originally introduced as an antispasmodic drug and has been used most widely in the urologic field. It apparently has a twofold action: namely, mild stimulation of the sympathetic nervous system plus direct relaxation of involuntary muscles and constriction of the blood vessels. We have administered it hypodermically in doses of 100 to 200 mg. to 18 different patients suffering from headaches which fit the general "migrainous" pattern. All of these patients suffered from recurrent unilateral headache, usually beginning early in the morning, accompanied by nausea with or without vomiting. In all of them there is a familial history of similar headaches. All but two of the patients were women.

Once the diagnosis of migraine has been established a test dose (50 to 75 mg.) of Octin should be given with the patient under close supervision. The drug should not be given to patients with hypertension, but fortunately the blood pressure in most patients with migraine tends to be low. A few patients with unstable vasomotor systems do respond with an excessive hypertension to the injection of Octin. This hypertension develops within 10 to

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† "Octin," manufactured by the Bilhuber-Knoll Corporation, of Orange, N. J., who kindly supplied the material for this investigation.

30 minutes after the injection and may persist for three to four hours. If the patient does not respond with an excessive degree of hypertension to this small dose, she is then instructed to administer such an injection to herself as soon as the headache begins to appear. Approximately half of the patients so treated will achieve prompt and dramatic relief of the pain, frequently within 10 to 15 minutes after the injection. So far we have been unable to predict in advance either from history or physical examination which patients will obtain relief and which ones will not. When relief is obtained it usually can be reproduced with subsequent headaches. The dose necessary to produce relief varies among different patients between 100 and 200 mg. The oral administration of 130 to 200 mg. of Octin mucate has occasionally been helpful.<sup>2</sup>

It should be reemphasized that the individual response to this drug varied tremendously. We have seen no serious untoward effects from the 100 mg. dose, but the larger doses occasionally produce palpitation, hypertension, dizziness, and even syncope. The occasional patient who requires relief from headaches two or three times weekly may develop a general increase in "nervous tension" and palpitation, but this can usually be controlled by small doses of sedatives. One patient under our management has received 113 injections of Octin in doses of 150 to 200 mg. during a period of 15 months. She has shown no toxic symptoms aside from slight nervousness, and relief of the headache continues to be prompt and complete. She has at no time developed hypertension subsequent to the injections. On the other hand, several patients have had rises in blood pressure from a normal of 100 mm. of Hg systolic and 70 diastolic to as high as 185 systolic and 110 diastolic within 30 minutes after the injection of 150 mg. We do not recommend the use of the drug in patients who respond in this way.

Toxicity experiments on animals have been carried out by Drs. R. P. Walton and C. B. Preacher<sup>3</sup> and have not shown any appreciable deleterious effect.

It is obvious, therefore, that this drug is not suitable for the treatment of all patients suffering from migraine headache. However, in those patients in whom it produces prompt relief and in whom it does not produce any hypertensive effect, its superiority over other drugs so far employed for the symptomatic relief of this condition is considerable. It does not produce nausea and vomiting, nor does it cause peripheral vasoconstriction in the hands, which occasionally is annoying in patients treated with ergot. When used with caution and careful control in properly selected patients it offers significant advantages in the symptomatic control of migraine.

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## BRUCELLA SENSITIZATION: A CLINICAL EVALUATION \*

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IN a recent paper dealing with the laboratory diagnosis of undulant fever, Lee Foshay,<sup>9</sup> when discussing the chronic types of the infection, made the following significant statement: ". . . We must expect many current diagnostic errors due to imperfect understanding of the clinical aspects of the disease, to imperfections in our laboratory tests, to misuse of these tests and to misinterpretation of their results."

A comprehensive review of the literature as it pertains to chronic brucellosis,<sup>3, 4, 6, 7, 14, 15, 17, 18, 19, 25, 27, 29, 30, 31, 37</sup> while impressive as to evidence favoring the frequent occurrence of a low grade, chronic form of the infection, makes one feel that there is much truth in Foshay's statement and leaves one with a strong desire for a better understanding of the disease. From the clinical standpoint—that is of proved chronic cases—two facts are impressive: the subjective findings are conspicuous because of their multiplicity and variability; the objective findings are conspicuous because of their absence. Such being the case, the desirability for reliable laboratory diagnostic criteria at once becomes apparent. While the tests in vogue may each have a sphere of usefulness, many imperfections and limitations complicate their indiscriminate use.<sup>1, 3, 8, 9, 17, 20, 21, 22, 23, 24, 25, 26</sup> All authorities agree that the recovery of the organism constitutes the only positive proof of brucella infection but that this is rarely accomplished in the chronic case. Although a high serum agglutinin titer is generally accepted as good presumptive evidence of active infection, the use of the agglutination reaction in chronic brucellosis appears to be of very indefinite value. If negative, as it usually is, it does not exclude brucella infection, and if positive, it is apt to be so in very low dilution. There is lack of agreement as to whether or not agglutination in low dilution is of specific significance. The results of the test may vary in different hands because of variations in technic and antigen. Finally there is disagreement as to what constitutes the transition level between a "low" and a "high" titer. The opsonocytophagic reaction has been attractive to all investigators. From the technical standpoint, however, its reliable performance is difficult. There is no unanimity of opinion as to its significance and its interpretation is often at variance with other and more reliable clinical and laboratory data. Of all the laboratory procedures used in the study of chronic brucellosis, the one most consistently positive

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is the intradermal reaction to brucella antigen. While an occasional false positive reaction may be obtained, most authorities agree that a positive reaction is a reliable indication of a state of brucella allergy. Its use is chiefly limited by the fact that it does not distinguish past from present, or latent from active infection, and also by the fact that an occasional infection fails to result in demonstrable sensitization. A positive skin test does not establish the diagnosis of brucellosis.

If the above discussion constitutes a fair statement of the diagnostic difficulties in chronic brucellosis and, on the other hand, if the assertion is true that the disease is a common cause of chronic illness, it is apparent that there is great need for careful study, from both clinical and laboratory standpoints, of large groups of individuals suspected of brucella infection. In such an investigation the solution of two problems is desirable: a satisfactory method of case finding and the establishment of control groups. Conditions for such an investigation would be ideal if, by the routine application of easily performed, well standardized and well understood tests, the actively infected could be readily identified. There is as yet no method of case finding on these terms but if the investigation be broadened so that brucella allergy instead of active infection be the basis for case selection, then there is a fairly reliable test—the intradermal reaction to brucella antigen. Comparisons of duplicate data from the resultant sensitive and nonsensitive groups will then serve to satisfy the need for control observations.

Table 1 summarizes the source and status of the individuals that we have tested to date. Intradermal tests were performed with Huddleson's Brucel-  
lergen on two groups. The first group consisted of 1497 adult patients, all having presented themselves for examination because of some health problem

TABLE I  
Source and Status of Subjects Tested

	Number tested	Number positive reactors	Per cent positive reactors
Chronically ill patients			
Private practice: Darley and Gordon	1497	236	15.76
Control or well group			
Physically well patients: Colorado Psychopathic Hospital	239	21	8.76
Maternity patients: Colorado General Hospital	222	21	9.90
Students: University of Colorado	419	46	10.97
Employees: Gates Rubber Company	290	32	11.03
Total	1170	120	10.25
Percentage difference between patient and control groups:			5.51

—usually one of long standing. The clinical findings in each case were recorded on form history and physical examination sheets so that the initial work-up was uniform. Adequate laboratory and consultation facilities were available so that the clinical investigation in each instance was complete. Of these 1497 patients, 236 or 15.76 per cent were found brucella sensitive.

The second or control group was made up of 1170 well individuals. One hundred twenty or 10.25 per cent gave positive tests. When this percentage is contrasted with that of the patient group, a difference of 5.51 per cent will be noted. The statistical evaluation of this difference yields a value of 4.24 standard deviations, a figure well above that of the two standard deviations necessary to be of significance. Since more of our controls were under 30 years of age than over and since the reverse was true for the patient group, we have set up table 2 to show the incidence of positive reactors in

TABLE II  
Breakdown of Patients and Controls into Subgroups above and below Thirty Years of Age  
(The totals are less than those given in table 1 because the ages were not known for all individuals tested)

Twenty-nine and below			
	Number tested	Number positive	Per cent positive
Patient group:	296	43	14.52
Control group:	862	85	9.97
Percentage difference:			4.55
Thirty and above			
	Number tested	Number positive	Per cent positive
Patient group:	1166	193	16.55
Control group:	268	31	11.56
Percentage difference:			4.99

the two groups for both below and above this age level. The percentage difference between the controls and the patients under 30 years of age was 4.55 and over 30, 4.99. From the statistical standpoint these two figures are just barely at significant levels: the values being 2 and 2.1 standard deviations respectively. It should be stated, however, that these values will become more significant if, in each comparison, the percentage difference does not diminish as the smaller group approximates the larger in size.

It has been pointed out that case selection by intradermal testing will include not only those individuals with active infection but also those whose infections are latent or inactive. At first glance it may appear that the inclusion of positive reactors of the latter two types might dilute any significant data from the first type. The degree to which this may be true depends upon the frequency of the chronic form of the infection. If chronic

brucellosis is at all common, in a study involving a large number of brucella sensitive cases, the emergence of significant trends should not be obscured, particularly since it would be probable that the incidence of active infection would be high in a group of chronically ill, brucella sensitive patients. On the other hand, since brucella sensitization does frequently occur as an incidental finding, any such trends, to be considered significant, must be definite.

Aside from the general statement that chronic brucellosis may constitute a clinical entity in itself, the literature states or implies that the infection may cause or aggravate such syndromes as the allergies,<sup>6</sup> the chronic arthritides<sup>11, 12, 13</sup> and the psychoneuroses.<sup>20, 33, 34, 35</sup> If these statements and implications are sound, it would seem logical to expect the incidence of brucella sensitization to show an increase in association with such conditions. The balance of this report will deal first with findings relative to the possibility of any relationship between brucella sensitization and allergy, chronic arthritis or psychoneurosis and, finally, with evidence that may support the existence of a low-grade, indolent form of chronic brucellosis as a clinical entity.

Dustin and Weyler<sup>6</sup> felt that clinical and laboratory evidence justified a diagnosis of chronic brucellosis in 441 patients. In this group all had a history of allergy in their immediate families. The incidence of personal allergy was 92 per cent. No control observations were noted, no comments as to the types of allergy were included and no attempt was made to interpret the significance of the finding except to correlate it with other observations which they felt justified the conclusion that the symptoms of chronic brucellosis were due to brucella allergy rather than to lowered resistance. One feels the implication, however, that these investigators believe that the individual who has an inherent allergic tendency has thereby an increased susceptibility to brucella sensitization and, a priori, to chronic brucellosis. Although their concept regarding the symptomatology of chronic brucellosis may be plausible, our observations indicate that neither allergy in the immediate family nor personal allergy has any association with sensitization to brucella. By using the most reliable index to family allergy—a family history of hay fever, we found the incidence to be essentially the same in both the sensitive and nonsensitive groups: 13.9 and 13.8 per cent respectively. For the sake of accuracy in our consideration of personal allergy, only diagnoses based upon our own observations were included. Inspection of table 3 makes it apparent that the conditions most commonly regarded as allergic in nature likewise showed no essential differences in frequency between the skin test negative and the skin test positive patients. Migraine is not considered in the study because we feel that it is a symptom complex in which many factors other than allergy may be involved.

The neuroskeletomuscular manifestations in cases of acute and subacute undulant fever are well recognized but any consistent relation between the chronic forms of the infection and the chronic arthritides is questionable. In 1938 Goldfain<sup>11</sup> gave impetus to the consideration when he reported evi-



TABLE III  
Allergy Tabulation

	Skin test negative patients			Skin test positive patients		
	Number patients considered	Number cases found	Per cent cases found	Number patients considered	Number cases found	Per cent cases found
Family allergy						
Hay fever	1197	166	13.8	236	33	13.9
Personal allergy						
Hay fever	1261	202	17	236	45	19.1
Asthma	1261	103	8.1	236	15	5.2
Neurodermatitis	1261	82	6.5	236	10	2.3
Urticaria	1261	73	5.8	236	21	8.8

dences of brucella infection in 51 per cent of 157 patients, a preponderance of whom were suffering with arthritic disease. He did not indicate the frequency of the various types of joint conditions but, in another publication<sup>12</sup> dealing with 50 arthritic patients, he reported brucella sensitization in 13 of 19 patients with atrophic arthritis, one with ankylosing spondylitis and seven out of 10 with hypertrophic arthritis. No control observations were included in his reports.

Evidence indicating any significant association of brucella infection and the atrophic type of arthritis has not been uncovered by other investigators. At the 1940 meeting of the American Rheumatism Association we<sup>5</sup> presented evidence against any significant association of brucella sensitization and atrophic arthritis. Green and Freyberg,<sup>16</sup> after careful investigation of 25 patients with atrophic arthritis, were able to demonstrate brucella sensitization in but two instances. Manchester<sup>25</sup> reported 13 per cent of 48 cases of rheumatoid arthritis with positive skin reactions but, after demonstrating sensitization in 11 per cent of 175 nonarthritic patients, he concluded, as did Green and Freyberg, that brucella infection could not be of etiologic significance in this type of joint disease.

Our data underscore the conclusions of Green and Freyberg<sup>16</sup> and of Manchester,<sup>25</sup> for only six, or 7.5 per cent of 80 patients with classical atrophic arthritis gave positive reactions to intradermal brucella antigen. This figure is far below the incidence of positive reactions in our control group of 1170 well individuals. While Goldfain<sup>13</sup> has reported brucella sensitization in five of 18 patients with ankylosing spondylitis, we obtained no reactions in six patients with this condition.

Atypical rheumatoid (subacute infectious, focal infection) arthritis is the one type of arthritis in which the demonstration of brucella sensitization might logically be expected to point the way, at least occasionally, to etiology. Sixty-one of our patients had atypical rheumatoid arthritis and, of these, 11 or 18 per cent were brucella sensitive. This figure, when compared to the 10.25 per cent incidence for the control group, may seem impressive. Three

of the cases were particularly of interest from the brucella standpoint because of their improvement from specific therapy. We feel that a large series of brucella sensitive patients with this type of arthritis should be studied carefully from the cultural and therapeutic standpoints in order that the possible rôle which brucella infection might play in the etiology of the condition might be thoroughly considered.

One of Goldfain's reports<sup>12</sup> hints at a possible relationship between brucella infection and hypertrophic arthritis. Of 1261 skin test negative patients, we found this type of arthritis in 205 or 16.5 per cent, and in 236 skin test positive patients we found the condition in 42 or 17.8 per cent. These two figures are too close to permit any conclusion other than that brucella infection and hypertrophic arthritis have no significant relationship.

Although brucellosis does not appear to be of importance as a cause of chronic arthritis, the literature carries the strong suggestion that subjective rheumatic complaints without objective evidences of joint disease occur with significant frequency in brucella sensitive patients. Angle and Algie<sup>1</sup> reported rheumatic symptoms in 34 per cent of 462 brucella sensitive grade and high school children as against only 6 per cent of 100 skin test negative controls. Calder<sup>4</sup> indicated that joint pain and swelling occurred in almost 50 per cent of 550 patients giving positive reactions to intradermal brucella antiserum, a skin testing material of questionable value. The frequency of cases with objective joint findings was not indicated and no control observations were included. Green and Freyberg<sup>16</sup> obtained positive reactions in nine of 25 patients selected because of rheumatic symptoms and manifestations not characteristic of any of the common types of arthritis. Although all of these nine patients complained of myalgias and arthralgias, none presented physical signs of joint disease. While testing 100 patients with miscellaneous chronic complaints, Manchester<sup>25</sup> found 38 with positive reactions, 55 per cent of which had joint symptoms. He regarded this as significant since only 20 per cent of the 62 skin test negative patients had similar complaints.

Any investigation designed to shed light upon this question must take into account the fact that subjective neuroskeletal muscular complaints without objective evidences of disease are very common in the psychoneuroses. This fact is emphasized by our finding that out of 100 brucella negative patients with personality determined illness, 54 had such complaints (table 4). Consequently, patients with emotional factors in their illnesses were excluded from the groups involved in the following data. As will appear later we have carefully selected 74 skin test positive patients in whom we felt a diagnosis of chronic brucellosis was justified. Muscle and joint discomforts were present in 65 per cent of this group. For control purposes we selected a group of 110 skin test negative patients with no objective evidence of any type of joint disease. Subjective rheumatic symptoms were present in 38 per cent of this group—a figure sufficiently below the 65 per

TABLE IV  
Symptom Tabulation  
(Figures expressed as per cent)

Symptoms	74 cases of probable brucellosis	62 cases of psycho- neurosis, brucella positive	100 cases of psycho- neurosis, brucella negative
Fatigue, weakness	80	77	81
Neuroskeletomuscular discomfort	65	63	54
Back ache (including neck)	32	45	40
Low	24	32	32
Interscapular	8	5	
Neck ache	7	8	8
Joint pain	26	26	21
Generalized aching	22*	13	14
Neuropsychiatric	57	79	76
Emotional instability	7	30*	30*
Irritability	26	34	32
Tension, anxiety	19	53*	55*
Depression	23	30	17
Insomnia	23	40	26
Headache	43	58	66
Migrainous	11	13	15
Non-migrainous	36	50*	51*
Digestive	40	59	81
Constipation	19	35*	33*
Indigestion	30	51*	59*
Diarrhea	5	3	6
Fever	34*	8	11
Nasal congestion	31	27	38
Dizziness	24	23	40
Sweating (spontaneous)	23*	14	24
Heart consciousness	20	47*	30
Chilliness	13	3	18
Urinary	13	14	25
Paresthesias	12	24*	27*
Abdominal pains	12	30*	38*
Chest pain (not anginal)	11	13	18
Menstrual (female patients)	28	45*	46*
Pain	19	30	25
Excessive flow	9	22	10
Scanty flow	5	5	7
Irregularity	2	10	4
Miscellaneous data (values not expressed as per cent)			
Number females	43	40	67
Number males	31	22	33
Average age (years)	35	44	37
Average number of symptoms	6	8*	8*
Average duration of symptoms (years)	3.5	8*	5.8*

\* Figures considered of significance.

cent noted for the brucella sensitive group to be impressive as far as the association of brucella sensitization and subjective neuroskeletal complaints is concerned.

In an article published in 1934, Alice Evans,<sup>7</sup> in writing of chronic brucellosis, made a series of significant statements: "... the textbook definition of neurasthenia describes chronic brucellosis: exhaustion, insomnia,

irritability and complaints of aches and pains for which no objective signs can be found. . . . There is no doubt that chronic brucellosis is often diagnosed as neurasthenia. . . . These facts challenge the right of a physician to make a diagnosis of neurasthenia . . . without considering . . . the possibility of chronic brucellosis."

Since 1934 most authors dealing with the subject of brucellosis have referred to and have agreed with the essence of these statements. A few have gone further and have considered brucella infection as a major cause of neurasthenia.<sup>20, 33, 34, 35</sup> Although such a wholesale viewpoint disregards the accepted concepts of psychopathology, the superficial clinical resemblance of chronic brucellosis to neurasthenia, and to the other psychoneurotic reaction types, justifies analysis and discussion. In table 4 will be found a comparison of the symptomatology of our group of 74 patients with probable brucellosis with that of 100 skin test negative psychoneurotic patients which emphasizes the clinical similarity of the two groups. In addition to this symptom similarity, it should be pointed out that paucity of objective physical findings and static chronicity were equally common to both.

It is possible that a chronic infection such as brucellosis could help lessen resistance and contribute to conditions which might favor the development of neurotic symptoms or of a neurotic attitude. Neurotic symptoms do not necessarily in themselves reflect a clinical psychoneurosis, but a situation responsible for neurotic symptoms, particularly if a neurotic attitude has developed, can readily lead to a personality determined illness. Finally, since brucella sensitization is so common and since chronic brucellosis itself may also occur frequently, the occurrence of both sensitization and active infection in the psychoneurotic is inevitable. In other words, given a brucella sensitive patient with neurasthenic symptoms, one may be confronted with a real problem in differential diagnosis. The patient may have chronic brucellosis or psychoneurosis or both. The presence of one does not rule out the possibility of the other. However, if brucella infection is commonly involved either as a primary or as an aggravating cause of personality determined illness, it would be reasonable to expect brucella sensitization to be decidedly increased in a large group of such patients. If this line of reasoning is correct, our findings oppose the premise that brucellosis is a very significant factor in the etiology or aggravation of the psychoneuroses. We considered that emotional and personality factors were playing a significant rôle in the illness of 702, or 46.9 per cent of the 1497 patients skin tested to brucella. Of these 702 patients, 114 or 16.2 per cent were brucella sensitive. When compared with the 15.7 per cent positive incidence for the total group of 1497, this figure is robbed of any significance. This conclusion is further borne out by a comparison of the number of psychoneurotic patients in the brucella negative with the brucella positive group: 588 or 46.6 per cent for the former and 114 or 48.2 per cent for the latter. The difference between the two percentages is too small to warrant consideration.

If two fundamentally different conditions present a similar clinical picture, psychologic and therapeutic considerations make correct discrimination a matter of paramount importance. We consider this to be the case in the evaluation of brucella infection and personality malfunction. Every possible means for the differentiation of the two conditions must be resorted to. As has been pointed out in the introduction of this paper, much is to be desired from the brucellosis side of the problem because there are no reliable laboratory methods available for the selection of the actively infected case. From the psychiatric standpoint, the mental status examination<sup>32</sup> will, in the majority of instances, help with the evaluation of the patient from the personality standpoint. Careful judgment is essential. In general it is our conclusion that given a brucella sensitive patient, a personality determined illness must be considered before a diagnosis of chronic brucellosis should be seriously entertained. In other words, a diagnosis of chronic brucellosis should be challenged until the possibility of psychoneurosis has been evaluated.

The final object of this paper is to establish evidence for or against the existence of a low-grade indolent form of brucellosis as a clinical entity in which, except for the usual presence of skin sensitivity, confirmatory laboratory findings are frequently indeterminate or absent. In other words, can the demonstration of brucella sensitization to any degree serve as a foundation for the selection of patients in whom a clinical diagnosis of chronic brucellosis is to be seriously considered?

In order to isolate the cases of brucella sensitization most likely to have active infection, it was felt necessary to consider only those cases in which every other possible significant diagnosis had been excluded. Diagnosis by exclusion is not a sound clinical principle, but as far as this investigation is concerned, we felt that it was the only approach for the selection of the actively infected from a fairly large group of brucella sensitive patients. It is probable that many patients were discarded in whom active infection may have been an illness factor. Thus, of 236 patients found to be skin test positive, all but 49 were omitted from consideration as possible cases of chronic brucellosis because of other disease or findings that could have accounted for their complaints. To this 49 it was possible to add another 25 patients selected just as carefully from cases referred for consultation because of positive reactions to intradermal brucella antigen. Thus a total of 74 cases of probable chronic brucellosis was available for clinical study. The data have been organized with the view of identifying any symptomatology that might characterize an indolent type of the infection. The symptomatic tabulation of the 74 patients is given in the first column of table 4. The most common symptoms are listed in the order of their frequencies. Since it was apparent that the symptom pattern was very similar to that often found in the psychoneurotic patient, a similar tabulation for 100 skin negative psychoneurotic patients was added for comparison. Comparison of the brucella positive with the psychoneurotic group reveals the same symptom

order and, with few exceptions, no striking differences in symptom frequency. Generalized aching, low-grade fever and spontaneous sweating were more frequent in the brucella group, whereas psychic and nervous symptoms, non-migrainous headache, digestive symptoms, heart consciousness, abdominal pains, paresthesias, menstrual disturbances and a greater number and duration of complaints were more common to the psychoneurotic patients. As far as individual symptoms were concerned, it was not felt that anything peculiar or constant that would differentiate either group was apparent.

Physical examination of all patients included in the tabulation, brucella positive as well as psychoneurotic, revealed no findings of significance.

A comparison of our data with the literature dealing on the one hand with proved brucellosis and on the other with other clinical studies of brucella sensitization, should be of interest. Table 5 represents an effort to

TABLE V  
Comparative Symptom Tabulation  
(Figures expressed in per cent)

	Proved brucellosis	Studies of brucella sensitization					
	Hardy* 300 cases	Calder* 550 cases	Manchester*		Darley and Gordon 74 cases	Angle and Algie	
			38 cases	62 controls		562 cases	100 controls
Fatigue, weakness	100	89	45†	50†	80		
Neuroskeletomuscular			53	17	65	34	6
Back ache	47	63			32		
Neck ache	28	57			7		
Joint pain	33	49			26		
Generalized aching	43	66			22		
Neuropsychiatric	50	87			57	44	26
Insomnia	35	54			23		
Headache	63	69	25	4	43	37	15
Constipation	55	57	20	25	19	15	2
Indigestion			37	30	30		
Fever	100	85	25	2	34	5	1
Dizziness		18			24		
Sweating	83	49	17	1	23		
Chilling	78	51			13		
Abdominal pain	33	48			12		
Menstrual (female patients)		60			28		
Pain		42			19		
Excessive flow		30			9		

\* Figures transposed from a graph.

† Figure also includes "nervousness."

brief such a comparison. The study of Hardy et al.<sup>18</sup> represents a very complete clinical analysis of acute and subacute brucellosis. At the opposite extreme of infection level is the contribution of Angle and Algie<sup>1</sup> who reported the mass symptomatology for 462 brucella sensitive school children. These investigators found a much higher incidence of chronic complaints in this group than was found in 100 skin test negative controls. No effort was made to cull out the asymptomatic children, of which there must have been

quite a number. Consequently their figures may be lower than they would otherwise have been. We consider this work to be of considerable significance, not only because it was controlled but because positive allergic tests in children are in general of more clinical importance than they are in the average adult. Differences in the methods of classifying and tabulating symptoms complicate the comparison but from the table it is apparent that the symptom frequencies for our group of chronic cases are intermediate between those for the acute cases of Hardy et al. and the sensitized cases of Angle and Algie. Furthermore, except for the fever, chills and sweats incident to the acute infectious state, the type of symptoms and the order in which they occurred were essentially constant throughout.

Four other reports, each in many respects similar to ours, deserve comment. For the sake of completeness we have attempted to add the symptom summaries from two of these to our table. While at first glance Calder's<sup>4</sup> data appear to be in general agreement with ours, we do not feel justified in stressing the fact because the reliability of antiserum as a skin testing material has yet to be established,<sup>9, 10</sup> because in all probability the figures are elevated due to the inclusion of many cases of acute brucellosis, because data were included from every patient giving a positive skin test regardless of the presence of other disease and finally because no control observations were reported. Manchester's<sup>25</sup> 38 cases of probable brucellosis are difficult to compare with ours because of a different type of symptom tabulation. Tiredness, easy fatigability and nervousness were listed together as a single category. The author did not indicate that psychoneurotic patients were excluded from his study and it may be that the higher incidence of these symptoms in his control group was due to the inclusion of such patients. A third paper by Griggs<sup>15</sup> and a fourth by Urschel<sup>37</sup> together cover an aggregate of 153 patients who presented essentially the same order and frequency of symptoms as noted for our group of patients.

After first excluding every other possible explanation for symptoms, the skin testing of patients presenting a picture similar to that which we have reported in our 74 cases should constitute a good test of the case which we have tried to establish for "indolent brucellosis." The literature yields two reports of such an approach to the problem and in each instance we consider that a significant score was obtained. As has been mentioned, Manchester found 38 positive reactors in 100 patients all of whom before testing presented a picture compatible with a diagnosis of chronic brucellosis and similarly Urschel<sup>37</sup> found 70 positive reactors among 124 such patients (56.4 per cent).

Before the consideration of any laboratory observations, we again wish to emphasize that our grouping of brucella sensitive patients was based entirely upon clinical grounds. It was not until after the groups had been established that the results of agglutination tests were tabulated and credited to each group. The rapid technic with concentrated antigen was the method used, only agglutinations performed before intradermal testing were re-

corded and all positive reactions, weak or strong, were tabulated. Table 6 contains the summary of the results. Attention is first called to the finding that positive agglutinations were obtained in only 7.26 per cent of all the skin test negative patients as compared with 38.3 per cent for all of those skin test positive. To us, however, the most significant finding was that of positive agglutination reactions in 50.8 per cent of the patients whom, from the clinical standpoint, we felt were the most likely candidates for active chronic brucellosis. The results of the opsonocytophagic tests were not tabulated according to groups because of 177 tests, 164 or 92.5 per cent gave readings

TABLE VI  
Tabulation of Agglutination Reactions

	Num- ber of tests	Number positive according to agglutination titer					Total number positive	Per cent positive
		1-25	1-50	1-100	1-200	1-400		
Skin test negative patients	1010	20	31	21	1		73	7.26
Skin test positive patients	217	12	27	24	12	8	83	38.3
Cases of probable brucellosis	61	3	10	10	3	5	31	50.8
Cases of psychoneurosis	40	1	2	3	1		7	17.3
Cases discarded	116	8	15	11	8	3	45	38.8

low enough to indicate very little or no immunity. Blood cultures, the few times taken, were negative.

We feel that a review of our data seems to favor the entity of "indolent brucellosis" but in doing so it emphasizes that while certain clinical and laboratory characteristics may appear rather definite for a group of such cases, they are not marked enough to be of practical help when it comes to the consideration of the individual patient. Consequently it is again emphasized: given a brucella sensitive patient, a diagnosis of chronic brucellosis can not be seriously regarded as probable until every other possible explanation for symptoms has been carefully considered.

#### CONCLUSIONS AND SUMMARY

Of all the laboratory methods available for the study of chronic brucellosis, the one most consistently positive is the intradermal test. The indiscriminate use of this test, however, is limited by the fact that it does not distinguish past from present or latent from active infection. In spite of these limitations, our finding that brucella sensitization occurred significantly more often in the chronically ill than in the well, would seem to indicate that brucella infection was frequently involved in chronic ill health and also that sensitization must to a considerable degree parallel active infection.

Using these premises as a working basis, it was our purpose to make a careful clinical analysis and study of a large group of patients skin tested with brucella antigen in order to determine first, if brucella infection could be involved as an etiologic or aggravating factor in such conditions as the



allergies, the chronic arthritides or psychoneuroses and second, if a low-grade, indolent form of brucellosis could be identified as a clinical entity.

As to the first consideration, our data were opposed to any idea that brucella infection might be of etiologic or contributory importance in allergy, chronic arthritis or psychoneurosis. In the discussion of joint disease, however, a plea was made for further investigation of the possibility in atypical rheumatoid arthritis.

The second consideration was based upon the concept that careful clinical study of the brucella sensitive patient can with reasonable accuracy establish the presence or absence of active infection. It was emphasized that every possible explanation for symptoms must be carefully considered before a diagnosis of chronic brucellosis is justified. In this regard, because of the superficial resemblance between psychoneurosis and what we consider chronic brucellosis, we feel that the former possibility should always be ruled out. We were able to present data from 74 patients in whom we felt a diagnosis of chronic brucellosis was probable. The most frequent symptoms encountered were: fatigue, muscle and joint aches and pains, non-migrainous headache, digestive complaints and low-grade fever. Significant physical abnormalities were conspicuous by their absence. The incidence of positive agglutination reactions was significantly high in the group. We feel that a discussion of our findings in the light of the available literature appears to favor a low-grade type of chronic brucellosis as a clinical entity.

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## HEPATIC CIRRHOSIS AS A COMPLICATION OF CHRONIC ULCERATIVE COLITIS\*

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THAT form of colitis which is generally called "chronic ulcerative colitis" is one in which a great many complications arise. This is not surprising in view of its chronicity, the marked structural changes which develop in the colon, the opportunity these afford for the spread of infection through the bowel wall, and the nutritional deficiencies which are so common during the prolonged course of the disease.

Most of the complications of chronic ulcerative colitis involve the colon itself, or the perirectal tissues, and include such well recognized conditions as polyposis, stricture of the colon, carcinoma of the colon, and perirectal abscesses. In addition to these, a number of systemic complications of chronic ulcerative colitis have been described. Bargaen, in listing 558 complications occurring in 1500 patients with chronic ulcerative colitis, makes mention of such complications as arthritis, cutaneous lesions, renal insufficiency, endocarditis, phlebitis, splenomegaly, ocular diseases (of which iritis is the most important), peripheral neuritis, progressive arterial occlusion, and multiple abscesses of the liver. The occurrence of nutritional deficiency as a complication of chronic ulcerative colitis has also been stressed (Mackie). This may be recognized by the presence of characteristic changes in the skin, tongue, and mucous membranes, by the development of edema, or by the demonstration by roentgen-ray of changes in the pattern of the small intestine.

It is rather surprising to note the rarity with which hepatic complications have been observed during the course of ulcerative colitis. Pylephlebitic abscesses of the liver are evidently strikingly infrequent, having been reported by Bargaen in only two of the 1500 patients reviewed by him. Others who have studied large groups of patients with ulcerative colitis have also encountered relatively few in whom hepatic disease could be demonstrated. Thus, such reviews of the disease as those of Bargaen, Jackman and Kerr, Feder, Hurst, Jankelson and his associates, and Streicher make practically no mention of liver disturbances associated with colitis. Although splenomegaly is mentioned as being found in some patients (in 14 of the 1500 of

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The majority of the patients reported in this paper were studied in the wards of the Graduate Hospital of the University of Pennsylvania, on the service of Dr. H. L. Bockus. We wish to thank Dr. Bockus for kindly permitting us to report these cases.

The peritonoscopic examinations mentioned in the case reports were performed by Dr. Wilbur W. Oaks.

Bargen's series) this has been usually considered to be a response to infection rather than the result of hepatic disease.

Comfort, Bargen and Morlock have reported four instances in which chronic ulcerative colitis was associated with hepatic insufficiency. All four of the patients had long-standing and relatively mild bowel disease with minimal anatomic changes in the colon. In three of these the colitis antedated the liver disease and in these three the colitis was thought to have been responsible for the development of the hepatic disturbance. These authors believed that injury to the liver by infection was of primary importance as a cause of the hepatic insufficiency.

Cain and Callen have been the only authors to emphasize the possibility that changes in the liver may be significant in the course of severe colitis and expressed the opinion that fatty hepatic degeneration appears often in the terminal stages of suppurative recto-colitis. Ratnoff and Patek, in their review of cirrhosis have quoted statistics from Oriental sources to the effect that in India, China and the Philippines the incidence of dysentery in patients with cirrhosis ranges from 25 to 40 per cent as compared with control series in which the incidence of dysentery was from 7 to 17 per cent.

Since hepatic disturbances of major significance have been observed so infrequently as complications of ulcerative colitis, we are reporting the following group of five patients.

#### CASE REPORTS

##### *Case 1. M. C. S. Female. Age 14.*

This patient was first admitted to the Graduate Hospital in April 1939. Diarrhea had begun one year prior to this. A diagnosis of amebic dysentery had been made, although the basis for this diagnosis is unknown. Seven months before this admission, pain had developed in the right upper abdomen. Because this was thought to be due to possible amebic abscess, laparotomy was performed. Empyema of the gallbladder was discovered and the liver was found to be small and cirrhotic.

Following this operation, the patient had remained well until August 1939 when diarrhea recurred. Examination at that time revealed marked emaciation, some peripheral edema, and abdominal distention. The liver was palpable across the epigastrium, and the spleen was found to be enlarged. Sigmoidoscopic examination revealed the mucosal changes of chronic ulcerative colitis.

The significant laboratory findings included reduction of the total proteins to 5.05 and of the albumin to 2.02, reduction of the total cholesterol to 83, of which the esters were 23 milligrams per cent, bromsulfalein retention of 4 per cent and a suspiciously positive galactose tolerance test (2.43 grams of galactose being excreted after the ingestion of 40 grams of the sugar).

Roentgen-ray studies of the small bowel revealed changes considered characteristic of avitaminosis and hypoproteinemia. Barium enema was not entirely successful, but the portion of the left colon visualized showed considerable mucosal pathology with polypoid hyperplasia in the region of the splenic flexure. The changes were considered diagnostic of chronic ulcerative colitis. The patient was discharged from the hospital on a program designed to correct the nutritional disturbances, but she continued to have severe diarrhea. Anorexia became pronounced and further weight loss resulted. Mild jaundice appeared. The patient was re-admitted for a few days in May 1940, quite toxic and febrile. Slight icterus was present. The tongue was

smooth and red. The abdomen was distended and definite ascites could be demonstrated. The spleen and liver were enlarged. The latter organ was firm and somewhat nodular.

Very few laboratory studies were performed. These revealed moderate anemia, extreme hypoproteinemia (albumin 1.99 grams per cent), a serum bilirubin of 3 milligrams per cent and bromsulfalein retention of 4 per cent.

Because the patient was considered to be moribund, her parents were permitted to remove her from the hospital. She died shortly after this. No autopsy was obtained.

*Comment.* This 14 year old patient had been found to have hepatic cirrhosis a few months after the onset of the symptoms of chronic ulcerative colitis. During the subsequent course of her illness, she developed splenomegaly, jaundice, enlargement of the liver, and evidence of liver dysfunction. The cirrhosis may have been responsible for the hypoproteinemia and the ascites, and may have also contributed to the difficulty of maintaining satisfactory nutrition.

*Case 2. J. M. Male. Age 45.*

Fourteen years prior to hospital admission, in September 1943, this patient had had a rectal operation of unknown character. For many years he had consumed large quantities of alcohol, and it is possible that his diet had not been adequate although information regarding this was indefinite. The general health had remained satisfactory until one year previously when a single rectal hemorrhage had occurred. There were no other symptoms until one month before admission when severe bloody diarrhea began. This was associated with fever, sweats and weight loss, but not with abdominal pain or tenesmus.

When admitted to the hospital the patient was quite toxic, and his temperature was 104 degrees. He was moderately emaciated and the tongue was red and angry in appearance. The heart was enlarged and a diffuse systolic murmur was heard. The abdomen was distended, but no ascites could be demonstrated. The spleen was palpable and the liver was definitely enlarged, being easily felt across the epigastrium. There was marked perirectal infection and numerous sinus tracts around the anus discharged pus. Sigmoidoscopic examination revealed a sanguino-purulent exudate in the rectum and sigmoid. The mucous membrane visualized was coarsely granular with numerous bleeding areas, and showed definite hyperplastic and polypoid changes. The initial diagnosis was acute fulminating recurrence of chronic ulcerative colitis, complicated by severe perirectal infection, sepsis and both hepatomegaly and splenomegaly. The presence of multiple liver abscesses was considered possible.

The significant laboratory findings (table 1) at this time included the demonstration of moderate anemia and of mild hyperglycemia, and also of slight hypoalbuminemia. Barium enema revealed diffuse ulcerative colitis with extensive polypoid changes.

Initial therapy consisted of a high protein, high caloric diet, with insulin for a short time, ample vitamin supplements, sulfasuxidine and liberal transfusions of blood and plasma. The immediate result was unsatisfactory. Evidence of a profound toxic state persisted and severe diarrhea continued. A peri-anal abscess formed, but evacuated itself. Gradually, however, there was a decrease in the severity of the symptoms, and some improvement in the patient's status. It was observed, however, that the liver had become larger and that its border was somewhat irregular. Peripheral edema appeared and the presence of ascites was demonstrated. Marked palmar erythema was also noted. Evidence of hepatic dysfunction was found in slight hyperbilirubinemia, bromsulfalein retention and lowered levels of both the total

TABLE I  
Laboratory Findings in Patient J. M. (Case 2)

Date	9/7	9/20	10/1	10/28	11/4	11/23	12/6	12/13	1/13	1/25	2/3	2/15	2/26	3/14	3/30	4/10
R.B.C. (Millions)	3.6	3.8	4.5	4.0	3.7	3.8	3.9	3.2	3.9	4.1	4.1	3.7	4.3	3.9	3.7	4.5
Total Protein	6.7	6.5	7.6	6.2	6.2	5.6	8	8	5.6	6.5	4.5	5.8	5.7	5.1	6	5.8
Serum Albumin	3.5	2.9	3.4	3.7	2.8	2.9	2.7	3.6	2.4	2.8	1.8	2.7	2.2	2.3	2.6	2.8
Serum Bilirubin			0.2	1.0	0.6	0.4		0.4	0.2	0.2		0.2	0.2			0.2
Total Cholesterol	188				134		146	150						106		109
Cholesterol Esters	73				64		100	95						60		71
Bromsulfalein Retention					6	15			17	8			15	10		
Cephalin Flocculation		2+				4+										4+
Prothrombin % Normal					75		45		61			61				

and esterified blood cholesterol. The serum albumin remained well below normal, despite high protein feedings and the liberal use of plasma and amino acids intravenously.

Although numerous diuretics were administered, the ascites increased so that it was necessary to tap the abdomen. The fluid obtained was clear and had the physical properties of a transudate. When the ascites re-accumulated, peritoneoscopy was performed. This showed no evidence of intra-abdominal malignancy. The omental veins were very distended. The picture presented by the liver was that of a pronounced cirrhosis with diffuse nodularity of the surface of the organ.

During the latter period of hospitalization, there was slight improvement in the patient's general condition. The diarrhea became less severe and the gross blood disappeared from the stools. The ascites decreased somewhat with the continued use of diuretics. As can be seen, however, from the following table, which lists the pertinent laboratory findings, liver dysfunction persisted and also the hypoalbuminemia, despite the administration of considerable amounts of blood and plasma.

The patient left the hospital on May 16, 1941 to continue on a high protein diet and vitamins. A few weeks later, however, he died rather suddenly. The details of the immediate cause of death are unknown.

*Comment.* This patient with severe fulminating colitis involving much of his colon also had definite cirrhosis. This resulted in enlargement of both the liver and spleen, ascites, and laboratory evidence of hepatic dysfunction. There was also persistent hypoalbuminemia. The diagnosis of cirrhosis was established by peritoneoscopy. The past history of this patient included alcoholism, associated with dietary deficiencies. The colitis may, therefore, not have been the only factor in the production of the cirrhosis.

*Case 3. M. S. Male. Age 51.*

When this patient was first seen in December 1943 he stated that he had had diarrhea for approximately 20 years. A diagnosis of chronic ulcerative colitis and rectal stricture had been made. The stricture was dilated but the diarrhea persisted, and over a long period the patient had up to 10 bloody movements daily. Finally, about two years before the original visit, the stricture was treated surgically, the patient was given sulfasuxidine and some improvement followed.

When the patient was first studied, the only significant abnormality was the demonstration by sigmoidoscopic examination of changes in the rectum and sigmoid,

quite typical of ulcerative colitis. Diet and sulfasuxidine were prescribed and, since there was symptomatic improvement, the patient discontinued visits. He returned in July 1945, stating that he had recently experienced intermittent mild diarrhea, but that weakness was pronounced and that a weight loss of 20 pounds had occurred. Sigmoidoscopic examination again showed evidence of moderately active colitis. A striking physical finding, however, was the presence of a large, firm and somewhat irregular liver. The spleen was not enlarged. There was neither edema nor ascites.

The laboratory studies revealed moderate anemia. The serum bilirubin was normal. A cephalin cholesterol flocculation test was positive. The hippuric acid synthesis was moderately reduced and there was 15 per cent bromsulfalein retention. Prothrombin time was normal.

Peritoneoscopy was performed. A small amount of ascites was found. The liver was uniformly enlarged, its surface was granular with small punctate hemorrhagic areas. A few larger nodules were seen. A biopsy taken from the right lobe of the liver demonstrated the presence of definite periportal cirrhosis.

Since the establishing of the diagnosis of cirrhosis, the patient had been treated with a high protein, high vitamin, smooth diet and vitamin supplements, liver injections and transfusions. It has been difficult to maintain a satisfactory blood count, although the diarrhea has been relatively mild and little blood is lost by bowel. Repeated laboratory studies indicate varying degrees of liver dysfunction as shown by fluctuating bromsulfalein retention and changes in the reaction of such tests as the cephalin cholesterol flocculation test and the thymol turbidity test. The liver has remained large and firm. No ascites has been recognized on physical examination.

*Comment.* This patient had had colitis for many years before liver disturbance was recognized. The first clinical evidence of the latter was the hepatomegaly and the presence of liver disease was then established by both laboratory studies and peritoneoscopy. Because the colitis had been present for so long before the development of cirrhosis, it is possible that the bowel disease contributed to the evolution of the cirrhosis.

*Case 4. A. B. Female. Age 60.*

This patient was originally admitted to the Graduate Hospital in October 1944. She had developed diarrhea three years before this during a period of intense nervous tension. It had recurred at relatively long intervals but during attacks the diarrhea was moderately severe, blood being passed with many of the movements. Despite the diarrhea the general health had remained satisfactory. There had been no weight loss.

General physical examination was negative, but the sigmoidoscopic findings were characteristic of active ulcerative colitis with moderate hyperplastic changes. Laboratory examinations showed mild anemia and hyperglycemia. The serum bilirubin and serum albumin and prothrombin time were normal. No detailed liver function tests were done at this time. Barium enema revealed the roentgen picture of ulcerative colitis involving the bowel distal to the hepatic flexure.

With treatment consisting of diet, rest, and sulfasuxidine, and investigations of some of the factors responsible for the nervous tension, there was prompt subsidence of symptoms, and the patient was discharged to the care of the family physician.

Following this period of hospitalization there were further recurrences of the diarrhea during periods of worry. Because of the marked severity of one of these recurrences, and the passage of numerous bloody stools, the patient was re-admitted to the hospital in January 1946. Physical examination was again essentially negative. The liver and spleen were not enlarged. Sigmoidoscopic examination, however, again showed active colitis.

A moderate anemia was present, but the blood sugar, serum bilirubin, and urine urobilinogen were normal. The serum albumin, however, was definitely decreased (to 2.49 grams per cent on one occasion), and the presence of hepatic dysfunction was indicated by bromsulfalein retention and positive response to the cephalin cholesterol, thymol turbidity and serum colloidal gold tests. The hippuric acid synthesis, however, was found to be normal. The barium enema again revealed colitis distal to the mid transverse colon with changes suggesting polypoid hyperplasia.

Peritoneoscopic examination showed no ascites. The liver was normal in size, its surface pale and studded with numerous uniform small nodules. The gross appearance of the organ was that of cirrhosis. Punch biopsy of the liver confirmed the diagnosis of cirrhosis.

On treatment such as had been given before, symptoms again subsided and the patient is now being treated with a smooth, high protein diet with vitamin supplements.

*Comment.* The diagnosis of cirrhosis in this patient was based upon the liver function tests, the peritoneoscopic examination, and the biopsy since there was no clinical evidence of hepatic disease. Because the cirrhosis was demonstrated in this patient after the colitis had been present for about five years, it is possible that the colitis may have contributed to the development of the liver disease.

*Case 5. L. G. Female. Age 23.*

Approximately six years prior to hospital admission in 1945, when the patient was 17 years old, she had experienced a change in bowel habit and had begun to have mushy stools. From time to time after this, short periods of bloody diarrhea occurred, particularly in association with nervous tension. The diarrhea had apparently never interfered with normal activities, and the patient had been considered well enough to enter the WAC, two years before admission to the Graduate Hospital.

Shortly after she entered the Army, a pustular rash appeared on the abdomen and extremities. No satisfactory diagnosis of the nature of this rash was reached, and it remained resistant to treatment. Three months after the appearance of the rash an illness characterized by fever and jaundice resulted in admission to an Army hospital. Roentgenogram of the colon, taken at this time, revealed changes later recognized as those produced by chronic ulcerative colitis. Because bowel symptoms were slight when these films were taken no significance was attached to these findings then. Despite various forms of therapy, low grade fever, slight jaundice, malaise, mild diarrhea and the rash recurred for prolonged periods during the two years that the patient remained in the Army. Because of the persistence of the illness she was referred to the Graduate Hospital in May, 1945.

At the time of admission, the temperature was 99° F., but this fluctuated considerably during the period of hospitalization, occasionally reaching 104° and usually being 100°. Pallor and inconstant jaundice were present. A few scattered papular and pustular lesions were noted over the lower abdomen and the extremities. The liver was enlarged, firm and smooth, but not tender. The spleen was also enlarged. The sigmoidoscopic picture was that of a moderately active chronic ulcerative colitis.

Moderate anemia was present and the serum albumin was consistently lowered to levels of between 3 to 3.5 grams per cent. The serum bilirubin fluctuated considerably, from 0.5 to 3.8 milligrams per cent. The total cholesterol was 164, the esters being 109. At admission the prothrombin time was decreased to 45 per cent of normal, but later rose to 75 per cent. A galactose test was border line positive (2.35 grams of sugar being excreted in the urine). The alkaline phosphatase level was elevated to 22 Bodansky units. There was definite bromsulfalein retention rang-



ing from 15 to 30 per cent. The cephalin cholesterol, thymol turbidity and serum colloidal gold tests were all strongly positive. Blood cultures and various agglutination tests were negative. Biopsy of the skin lesions and of a lymph node failed to reveal significant findings. By barium enema changes typical of chronic ulcerative colitis were demonstrated throughout the entire colon. There was no evidence of small bowel disease.

Peritoneoscopic examination showed both liver and spleen to be markedly enlarged. The liver was mottled and granular in appearance and presented the gross picture of cirrhosis. A satisfactory biopsy was not obtained.

Treatment consisted of rest and a high protein, low fat diet with vitamin supplements, transfusions and sulfasuxidine. There was some symptomatic response, but the febrile reaction persisted throughout the seven weeks that the patient remained in the hospital. From time to time diarrhea became more severe and sigmoidoscopic examinations then revealed evidence of increased activity of the colitis. The patient was discharged in June 1945 without definite improvement.

*Comment.* This patient presented evidence of marked hepatic dysfunction and a peritoneoscopic picture of cirrhosis six years after the apparent onset of her colitis. Although the colitis itself had not produced a great deal of disability, it was evidently more severe than was suggested by the diarrhea, because of the continued fever and the general ill health. The skin rash may have been a complication of the colitis. The colitis may have also been a factor in the evolution of the cirrhosis.

## DISCUSSION

These five patients in whom definite and advanced liver disease was found were encountered during a period in which 151 patients with chronic ulcerative colitis were studied. In our experience, therefore, the association of parenchymal hepatic disease with ulcerative colitis has not been unusual, although the paucity of reports on the association of these two conditions suggests that it occurs but rarely.

In four of these five patients, clinical evidence suggestive of the liver disturbance was noted during the period of treatment for the colitis. The possible presence of hepatic disease was indicated by such findings as enlargement of the liver, or of both the liver and the spleen, ascites and jaundice. In only one patient were there no clinical features such as these. In this case, recognition of the hepatic disorder depended upon the performance of liver function tests and subsequent peritoneoscopy.

The incidence of liver disease in cases with chronic ulcerative colitis may be even greater than our present report suggests. It is possible that the routine use of liver function tests would demonstrate that hepatic dysfunction exists in not a few patients with ulcerative colitis. At the present time, one of us (J. F. M.) is conducting a survey of patients with colitis to determine the frequency with which they suffer liver dysfunction of a sub-clinical degree. This survey includes an analysis of the value of the various liver function tests in the recognition of hepatic disorders in patients with colitis. We shall omit from this paper, therefore, a discussion of the relative merits of the different tests which were used in the study of these patients.

We believe, however, that mention should be made of the hypoalbuminemia which was found so consistently in the four of our five patients in whom the serum albumin level was determined. In the three of these who presented clinical evidence of liver disease, all of the determinations of serum albumin levels during the periods of hospitalization were well below the normal accepted by our laboratories (4 to 4.5 grams per cent). In the patient who had no clinical manifestation of hepatic involvement, the serum albumin was normal at the time of the original visit but dropped to 2.9 grams per cent at a subsequent admission.

Numerous disease conditions may, of course, lead to the development of hypoalbuminemia. This is not unusual in uncomplicated ulcerative colitis because of the frequency of inadequate food intake and the loss of protein substances in the bloody and purulent bowel discharges. We have been impressed in the past, however, by the prominence of hypoalbuminemia as a biochemical change in advanced liver disease and by the difficulty of restoring the serum albumin to a normal level when this had become lowered in the cirrhotic patient (Tumen and Bockus). Failure of response to measures which usually elevate the serum albumin level which has been depressed by nutritional deficiency or protein loss was a striking feature in the patients reported here. The hypoalbuminemia persisted despite a large protein intake and liberal administration of plasma and amino-acids by vein. This strongly suggests the importance of hepatic dysfunction in contributing to the hypoalbuminemia of these patients, and leads us to conclude that liver disease should be searched for in patients with ulcerative colitis who have decreased serum albumin that does not respond to the usual therapeutic measures. In a sense, persistent lowering of the serum albumin may be regarded as a "liver function test," and its demonstration should bring to the physician's attention the possibility of the co-existence of severe liver disease.

In four of the five patients reported here, full recognition of the presence of cirrhosis was made possible by peritoneoscopy. This method of examination proved entirely safe, even in patients whose general health had been seriously impaired by the presence of severe colitis. Our experience with these and other patients gives additional support to the confidence expressed by Benedict in the value of peritoneoscopy in the diagnosis of liver disease. When various laboratory procedures suggest that hepatic dysfunction, and possibly cirrhosis, may be present, peritoneoscopy is an invaluable procedure which can confirm or disprove this diagnosis quite rapidly and safely.

The finding of two such apparently unrelated diseases as ulcerative colitis and cirrhosis in the same patient calls for some study of possible connection between them. It must first be admitted that the two diseases may be unrelated to each other and that their association may be merely a coincidental one. Cirrhosis has been found in from 1 to 6 per cent of cadavers studied at routine autopsy (Tumen). In the case of our patient, J. M., alcoholism and dietary deficiencies may well have contributed to the development of

cirrhosis, even if he had never contracted his severe colitis. The discovery of cirrhosis in these five patients with ulcerative colitis, however, indicates to us that other factors than mere coincidence must be considered in attempting to explain the finding.

A few investigators have believed that severe colitis may be a manifestation of underlying liver disease. This opinion was expressed by Dimitresco Popovici and by Saccone and Repetto. These authors have stated that hepatic insufficiency is to be considered as the underlying disturbance producing the tissue changes which favor the development of colitis. They believe that the bowel disorder should be regarded as a local complication of the general systemic changes which have been produced by hepatic disease. The evidence presented in support of this opinion, however, has seemed to us to be rather inconclusive. The infrequency with which hepatic insufficiency has been observed in the past in patients with colitis is likewise against the viewpoint that a liver disturbance should be considered the primary cause of ulcerative colitis, as is also the fact that colitic disease has rarely been noted in the autopsy examination of patients dying of cirrhosis.

A study of our patients has convinced us, on the other hand, that severe and prolonged colitis may readily produce changes in the patient which lead to the development of cirrhosis. We, therefore, believe that cirrhosis may occur occasionally as a true complication of colitis. Some support is to be found for our opinion in the age and sex distribution of our patients, even though our group is admittedly so small that no statistical conclusion can be considered to be justified. Two of our patients were quite young, being only 14 and 23 years old. Cirrhosis at this age level is quite rare. Of the entire group of 151 patients with colitis, 68 were male and 83 were female. Of the five with cirrhosis, two were male and three were female. This sex distribution of the cirrhotic patients is perhaps not striking, but it does reverse the usual sex incidence of cirrhosis. The finding in this small group of patients with cirrhosis of two young individuals and of three women is at least suggestive of the possibility that the presence in these patients of ulcerative colitis may have contributed to the development of the cirrhosis.

The etiology of cirrhosis is still somewhat obscure. At present it is best to regard it as the end result of a variety of injuries to the liver—nutritional, toxic, infectious, and circulatory—rather than as a disease that is produced by the effect of a single agent. Recently, of course, great emphasis has been placed, and correctly so, on nutritional deficiencies as the cause for cirrhosis. Whether in the human, nutritional disorders alone can produce cirrhosis is not yet entirely clear.

In a patient with colitis, numerous factors conspire to furnish a background in which the development of cirrhosis need not be surprising. There is first, of course, the element of malnutrition, the importance of which in the colitis patient must be stressed again and again. Many patients with colitis receive inadequate diets. This is a result of anorexia, fear of certain

needed foods, and the lack of emphasis by the attending physician upon the need for a diet that is adequate in protein and all vitamins as well as in total caloric value. Bowel hypermotility and nutritional changes in the small intestine lead to faulty absorption of what food is taken. As a consequence of these factors, many patients with active ulcerative colitis admitted to a hospital can be shown to have signs of deficiency diseases which involve numerous organs, and which produce anemia and hypoproteinemia. An added cause of malnutrition and hypoproteinemia in the colitis patient, one that is usually unrecognized, is the loss of large amounts of protein substances in the discharges of blood, mucus and pus from the bowel. There are, unfortunately, few studies of this loss, but it is obvious that the amount of protein that leaves the body in this way can be very large. In determinations of protein loss by bowel of two patients, carried out by Monaghan, it was found that the daily rectal discharges contained from 25 to 30 grams of protein. Since one of these patients had had an ileostomy, and one was receiving nothing by mouth during the period of observation, it may be concluded that the amount of protein found in the rectal discharges came exclusively from the colon. The effect of continuous loss of this kind on the general body economy can be appreciated readily.

Ulcerative colitis usually runs a prolonged and chronic course. A victim of this disease can therefore suffer for long periods with deficiencies which injure the liver, finally to the point at which that organ is unable to play its part in the metabolism of proteins and vitamins. Secondary hepatic breakdown may then serve to perpetuate the nutritional disturbances which have contributed to its origin.

The general toxic state which often persists for so long in the colitis patient may also add to the injury of the liver. This is difficult to evaluate. The prolonged fever and general ill health contribute to the anorexia. They also increase the metabolic requirements and thus aggravate the nutritional defect. The toxic state may also induce mild degenerative changes in the liver which make it more susceptible to further damage by continued deficiencies. It is also necessary to mention the possible effect on the liver of the constant absorption of toxic material and bacteria from the bowel. This also is difficult to measure in any accurate way. The absorption of these materials, however, can be conceived as placing an added burden on the detoxifying functions of the liver as well as possibly directly injuring the liver cells. Further knowledge concerning the effect of the local bowel disease on the liver status must await more detailed studies of hepatic function in large groups of patients with colitis.

Finally it is necessary to inquire regarding the possible effect of the presence of the complicating liver injury on the course of colitis. Our five patients represented varying degrees of severity of colitis. In two of our patients the colitis was quite severe and the patients died within from 16 to 22 months after the appearance of colitic symptoms. In two of the patients the colitis was prolonged and resistant to treatment and the patient's general

health had been chronically impaired. In only one of the patients was the colitis of the intermittent and relatively mild type that responds fairly easily to rest, sedation, and similar general measures. This was the patient in whom there was no clinical evidence of liver disease, the presence of this being first suspected after the performance of liver function tests. In this patient, also, hypoproteinemia was not observed at the initial examination but was noted subsequently. There would seem to be, therefore, some rough parallel between the severity and ease of recognition of the liver disturbance and the severity of the colitis, although an investigation of a much larger group of patients is necessary before definite conclusions regarding this can be reached. It would not be unexpected, however, to find that the patients in whom severe liver damage exists are those with the more severe degrees of colitis. The presence of protracted bowel disease naturally leads to greater nutritional disturbance so that more marked liver injury is produced. This in turn increases the tendency to hypoalbuminemia and makes it more difficult to maintain the patients in protein and vitamin balance and preserve the satisfactory nutritional status so necessary for recovery from a disease such as ulcerative colitis.

### CONCLUSION

1. Among 151 patients with ulcerative colitis, five were encountered with cirrhosis. Two of these patients were much younger than those in whom cirrhosis is usually found, and three of the five were women.

2. In four of these five patients there was clinical evidence of the liver disease. In one there were no signs or symptoms of cirrhosis, but the presence of this was suspected because of abnormal responses to hepatic function tests. It is possible that routine use of liver function tests in patients with ulcerative colitis would reveal an even higher incidence of hepatic damage in this disease.

3. In four of the five patients the diagnosis of cirrhosis was established by peritoneoscopy, a procedure which proved safe and well tolerated in these individuals.

4. In four of the five patients the cirrhosis probably developed as a complication of the colitis. In the fifth patient it was difficult to conclude that this was the case because of an antecedent history of alcoholism and dietary deficiency.

5. A striking biochemical feature of the studies of these patients was the demonstration of hypoalbuminemia that persisted despite the strenuous application of therapeutic measures which ordinarily restore a lowered serum albumin level to normal. This suggests that hepatic disease is important in producing the hypoalbuminemia of these patients.

6. It seems probable that the development of cirrhosis in patients with colitis results chiefly from nutritional deficiencies, although the effect of general toxemia and of the absorption of toxic substances from the bowel

may be important in this respect. The nutritional deficiencies probably arise chiefly from defective diet and faulty absorption of proteins and vitamins. The loss of large amounts of proteins in the rectal discharges may, however, contribute significantly to the development of a deficiency state.

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# CARDIOLOGIC CRITERIA FOR THE DIAGNOSIS OF RHEUMATIC HEART DISEASE IN THE APPARENTLY HEALTHY SUBJECT\*

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THE cardiac manifestations of rheumatic fever have a special diagnostic importance for several reasons. First, they determine the importance of the disease to the health and life of the patient. Second, they are the sole manifestations which may persist in the patient after recovery from the acute phase. Finally, they are the only signs of rheumatic disease in the apparently healthy subject on the basis of which a foregoing episode of acute rheumatic fever may be recognized or suspected.

The application of cardiac signs to the diagnosis of rheumatic heart disease is complicated, however, by the difficulty in interpreting observed phenomena, and by the inconstant significance of some of the physical signs. Because of the obvious importance of diagnosing rheumatic heart disease when it exists, and of avoiding a mistaken diagnosis of this disease when it does not exist, it is the object of this paper to discuss the significance of the cardiac observations which may be the basis for a diagnosis of rheumatic heart disease.

The cardiac signs which may be found in the clinically inactive phase of rheumatic disease are residua of the signs which were present in the acute episode. Even when cardiac signs appear for the first time during apparent quiescence, in patients whose acute rheumatic episode produced no evidence of cardiac damage, they follow the same patterns as when the signs of cardiac involvement originated in an acute episode. Accordingly the interpretation and significance of these signs is in many respects the same in the acutely ill patient into whose differential diagnosis rheumatic fever enters as in the apparently healthy subject in whom a chance finding of an abnormal cardiac sign raises the suspicion of rheumatic heart disease.

The problem of evaluating cardiac findings will here be discussed primarily in terms of their implication as to the presence of heart disease in the apparently healthy subject. This evaluation is becoming increasingly important with the greater recognition of rheumatic fever as a problem in public health, for such findings occur not infrequently in the examination of new patients, in surveys of schools and communities or as chance discoveries in patients.

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A. *Diastolic murmurs.* These murmurs cause little difficulty in diagnosis since the two groups of murmurs heard in this phase of the cardiac cycle happen to be those which are almost invariably associated with organic valvular changes, mitral stenosis or aortic insufficiency.

1. The apical diastolic murmur as found in the apparently healthy subject is almost a certain indication of rheumatic heart disease and mitral stenosis. In the child it usually does not take the form of the classical crescendo presystolic rumble ending in the snap of the first mitral sound. More frequently it appears as a softer sound, mid-diastolic in time, rumbling in quality, which ceases before the first sound at the apex. However, in some children, especially those who have sustained considerable cardiac damage, it may appear in the classical "adult" form described above. This murmur may or may not be accompanied by an apical systolic murmur of mitral insufficiency, depending on the orifice of the stenosed valve.

A distinction should be made here between the active and inactive rheumatic patient. In the former a mid-diastolic murmur, blowing rather than rumbling in quality, may be heard at the height of an acute episode involving mitral insufficiency, and may regress and disappear leaving at most an apical systolic murmur as the patient improves. Under these circumstances a diagnosis of mitral stenosis cannot, of course, be made.

2. The aortic diastolic murmur is again pathognomonic of an organic valvular lesion, aortic insufficiency, and in the age groups in which luetic aortitis is quite unlikely it strongly suggests rheumatic heart disease. This murmur is again likely to appear in form somewhat different in children from that in adults. In children it may be heard only at the left border of the sternum in the third interspace, rather than at the classical aortic area. It also has a very hollow, sighing quality, as compared with the more low-pitched and full-bodied aortic diastolic murmur of adults. The direction of transmission of this parasternal diastolic murmur, when it is sufficiently intense, is in a diagonal line toward the apex. However, even when the examiner hears this transmitted murmur first at the apex its difference in quality from the somewhat rumbling apical diastolic of mitral stenosis should indicate its origin.

B. *Systolic murmurs.* These are more variable and difficult of interpretation.

1. The pulmonic systolic murmur. A systolic murmur, of a considerable range of intensity and pitch, may be heard in many normal hearts of children and young adults. In children it has been heard in as many as 60 per cent of normal subjects,<sup>1</sup> and among all age groups the data of the Medical Impairment Study of several life insurance groups showed only a 12 per cent increase of mortality among such subjects above the general expectation.<sup>2</sup> Since a pulmonic systolic murmur is a frequent normal finding, and since rheumatic pulmonic stenosis is very rare, no significance can be attributed to the pulmonic systolic murmur as a cardiac finding under the circumstances. It should be noted only for a baseline physical description of the subject.



Similarly in the acutely ill patient the finding of a pulmonic systolic murmur does not favor the diagnosis of rheumatic fever or, in the presence of definite signs of rheumatic fever, of rheumatic heart disease.

2. The aortic systolic murmur. Occasionally a systolic murmur may be heard at the second interspace to the right of the sternum. This may be accepted in children and young adults as evidence of aortic valve involvement by a rheumatic process. There are two exceptions to this conclusion, however. First it must be ascertained that this murmur is not merely transmitted from the pulmonic area. Second, in young adults, a very soft and labile systolic aortic murmur may be caused by the emotional tachycardia and hypertension of physical examination. This possibility can be tested by repeated examinations.

If no other explanation can be found for the presence of a systolic murmur in the aortic area and it is taken to indicate rheumatic involvement of that valve, such a finding does not constitute the basis for a diagnosis of aortic stenosis. The latter is rare, even in rheumatic hearts which have suffered a series of damaging episodes. The criteria for diagnosing aortic stenosis include a harsh aortic systolic murmur transmitted, with a thrill, into the vessels of the neck, low pulse pressure and left ventricular hypertrophy.<sup>3</sup>

3. The precordial twang. In many children a murmur is heard over the precordium, frequently including the area of the apex, which is also of no significance. This was perhaps best described by Still<sup>4</sup> as similar to the sound produced by the twanging of a tense string. A very low-pitched string of a bass-viol might also produce such a twang. The murmur is so low-pitched that it lacks a blowing quality. In fact its pitch is quite similar to that of the first apical sound itself, so that the effect is one of a prolongation of the first sound almost until the second sound, offering difficulty to the examiner in deciding precisely when the first sound really ends. This is in contrast to the case of the murmur of mitral insufficiency, in which the examiner hears the thud of the first sound give way to the more blowing effect of the murmur. This precordial twang is rarely recognized as such in general practice, probably because of the poor contrast in quality between the first apical sound and the succeeding murmur, and because little attention is directed to it in the literature. It is often either overlooked entirely by the referring physician where rheumatic heart disease is not otherwise suspected or is called an apical systolic murmur where there is suspicion of rheumatic disease. In the latter case, or when it is observed in routine examination, it has not infrequently been the basis for a mistaken diagnosis of rheumatic heart disease with mitral insufficiency. The likelihood of this misinterpretation is enhanced by the fact that this sound may be of moderate intensity, and that the point of maximum intensity, although usually in the midprecordium or somewhat below it, may be quite near the apex. As in the case of the pulmonic systolic murmur the presence of this

murmur does not favor the diagnosis of rheumatic heart disease in the well or ill subject.

4. Systolic murmurs at the apex. Systolic murmurs heard at the apex of the heart present the most difficult problems in the cardiologic diagnosis of rheumatic heart disease. A consideration of these murmurs emphasizes the importance of complete description of a cardiac murmur in terms which include quality, intensity, extent of transmission, point of maximum intensity and constancy. Some of these attributes make it possible to classify some of the murmurs heard at the apex in terms of their significance.

First, a systolic murmur heard at the apex may be the result of transmission of a pulmonic systolic murmur across the precordium. As the examiner explores the precordium for the point of maximum intensity of the murmur under these circumstances, the discovery that the sound is loudest at the base indicates that it has no more significance than the pulmonic systolic murmur.

Second, murmurs are not infrequently heard at the mitral area whose point of maximum intensity is to the right of the apex, either halfway to the sternal border or at that line. Although very little has been published of such murmurs it seems quite improbable that they have their origin in insufficiency of the mitral valve. Therefore these are also in all probability without significance for the diagnosis of rheumatic disease.

Third, there are murmurs heard at the apex which disappear or show marked variation in intensity in the course of the respiratory cycle, the cardio-respiratory murmurs. These are, of course, also without pathologic significance.

Finally there are soft murmurs heard at the apex in some cases of high fever, tachycardia and anemia. If correction of these features results in disappearance of the murmur they also are thereby shown not to imply disease.

On the other hand if a moderate or loud systolic murmur heard at the apex in the course of a routine examination is of maximal intensity at that point, of blowing quality, and transmitted toward the axilla it is probably well to assume that there is mitral insufficiency due to rheumatic heart disease.

The greatest difficulty arises in the case of the incidental finding of a systolic murmur maximal at the apex, of low or moderate intensity and blowing quality, transmitted very little or not at all to the left. In such cases no diagnosis can be hazarded until the following steps are taken.

1. Fluoroscopy in antero-posterior and oblique positions or teleroentgenography, to determine enlargement of the heart. If there is evidence of enlargement the murmur should be taken as evidence of organic disease of the heart. However, many subjects with mitral insufficiency do not show cardiac enlargement.

2. Electrocardiography. The electrocardiogram is of little value in inactive rheumatic heart disease, since only a small number of rheumatic

patients show changes in this stage. These may occasionally be residua of the changes which occurred in the active phase, or evidence of auricular hypertrophy or ventricular preponderance attributable to rheumatic lesions, but they cannot be said to be characteristic of rheumatic disease.

3. History. If a satisfactory history of a rheumatic episode in the past is elicited, the apical systolic murmur may be assumed to represent a residual mitral insufficiency. Such a history should include an authentic account of carditis, migratory polyarthritis or chorea by a physician, or a history of acute joint or muscle pains accompanied by obvious signs of infectious disease.

4. The laboratory findings associated with active rheumatic disease would not be of help here, since they are merely indicators of the presence of acute infection. However, in a subject in whom the cardiologic findings warranted a diagnosis of rheumatic heart disease an elevated erythrocyte sedimentation rate or leukocytosis might indicate some degree of activity of the rheumatic process at the time.

Unfortunately even if all of the above have negative results it is still not possible to say that the murmur may not be a residue of active rheumatic heart disease, and thus point to this diagnosis. A definite percentage of subjects with chronic rheumatic heart disease are unaware of a previous attack of rheumatic infection. Such patients, according to Scott<sup>5</sup> have been "variously estimated at 20 to 25 per cent" of all rheumatic subjects. This estimate is consistent with the data of Fineberg and Steuer<sup>6</sup> who followed for 6 to 15 years 100 children in whom only an apical systolic murmur was found. Thirteen per cent of the 45 children who had no history of rheumatic disease went on to further cardiac lesions, whereas the comparable rate among the children with such a history was 50 per cent, or four times as great. Even when a history is available, it is too often unsatisfactory, involving the patient's or his parents' description of joint or muscle pains, choreiform movements, rash, et cetera. Typical migratory polyarthritis, the one sign of rheumatic disease which is sufficiently dramatic to give rise to a satisfactory description by the layman, occurs in only a minority of all cases of rheumatic disease, comprising about a quarter of one series of 700 cases (Wilson<sup>7</sup>).

*C. Enlargement of the heart.* This physical sign, although it provides strong evidence per se of organic disease of the heart, will be only briefly mentioned here, because a rheumatic heart whose enlargement is sufficient in degree to be detected on physical examination will almost invariably have accompanying murmurs. In the usual sequence of events the examination by roentgen-ray for cardiac enlargement is carried out in an effort to provide evidence as to the organic nature of a murmur discovered on physical examination. In such cases evidence of enlargement of the left auricle or of either ventricle by the roentgenographic technics mentioned above makes almost certain the organic significance of the murmur.

A difficult problem arises in the management of subjects with unsolved apical systolic murmurs, that is, subjects without evidence of cardiac enlargement, electrocardiography, history of rheumatic infection, or transmission of the murmur. This group certainly includes some with damaged hearts, for life insurance statistics show a mortality of 56 per cent above the expected rate.<sup>2</sup> On the other hand certainly not all of these subjects have rheumatic heart disease, since the group who have a history of rheumatic fever or chorea to explain their apical systolic murmur show a mortality which is very much higher.

The diagnosis of a rheumatic heart disease cannot, then, be made solely on the basis of a systolic murmur confined to the apex. Nor does the correct management of the patient demand an immediate diagnosis, since the treatment is essentially the same in both cases. All such patients should be seen periodically at intervals varying up to six months, according to the circumstances of the case, with physical examinations at each visit and laboratory, roentgen-ray and electrocardiographic examination at longer intervals.

In the meantime the presence of the murmur as an adventitious sound which has not yet been fully explained should be made clear to the patient or to his parents, and the patient may be allowed normal physical activity except for competitive sports.

It is not possible to say how long such observation must be continued before the patient can be told that the murmur is without significance. If after a few semi-annual examinations there is no progression of the murmur or other evidence of rheumatic disease it is very unlikely indeed that rheumatic heart disease is present. Nevertheless there have been instances of recrudescence of rheumatic heart disease after many years. Even among patients who recovered from acute rheumatic fever with no trace of cardiac damage Bland and Jones<sup>8</sup> found as many instances of onset of cardiac signs in the second five-year period following the acute infection as in the first five years. There were a few cases in which cardiac signs appeared even in the second decade. Other studies have shown similar cases of long delayed reactivation.

The impossibility of making a definite decision as to the presence of rheumatic heart disease for a considerable length of time emphasizes the importance of following such subjects without creating the impression that they are "heart patients."

This discussion has emphasized rather more than might be expected the avoidance of a mistaken diagnosis of rheumatic heart disease, in comparison with the opposite error. There are two reasons for this. First, with the increasing attention which is being directed at rheumatic heart disease there will be increasing numbers of mass examinations, and school and community surveys, with the object of discovering unknown cases of rheumatic disease. The failure to classify properly the innocuous adven-

titious sounds and the failure to withhold a diagnosis where it cannot properly be made may create considerable confusion and in addition may ultimately do as much harm for many non-rheumatics as it will do good for the rheumatic patients discovered. Of a group of 11 children referred for study to the Rheumatic Clinic of the Philadelphia General Hospital as a result of one school survey, only three were found to have murmurs which were thought to have a possible pathologic significance. Second, the psychological effect on patient and family of a diagnosis of heart disease is so profound and far-reaching, and its effect on initiating cardiac neuroses so great, that it is essential to avoid such an effect when it is not necessary.

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# THE ACTION OF CARBON DIOXIDE IN WATER MOBILIZATION \*

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"ALTHOUGH changes in the properties and activities of cytoplasm probably explain many of the changes in distribution of body water, at present data are not available which permit a description in these terms. The least we can do is to cease speaking of the distribution of various ions as if they were always excluded from certain phases of body water," Darrow.<sup>1</sup> The previous statement is in complete agreement with that of Peters and his associates<sup>2</sup> who, as the result of their studies on "Osmotic Adjustments Between Cells and Serum in the Circulating Blood of Man," state: "Analysis of the experimental data presents only a paradox, . . . base traverses the cell membranes in a highly capricious manner which cannot serve the interest of osmotic equilibrium. . . . It is suggested that base may be transferred in behalf of cellular metabolism rather than osmotic pressure."

Since carbon dioxide is one of the most common products of tissue activity we have focused our interest on this product. From our observations we have been forced to conclude that the accumulation of carbon dioxide within the tissues results in increased hydration, while the decrease of carbon dioxide is accompanied by decreased hydration.

## THE EFFECT OF DECREASING CARBON DIOXIDE

*Hyperventilation.* During hyperventilation there occur: (1) a fall in carbon dioxide tension of the alveolar air, (2) a decrease in the carbon dioxide combining power of the venous plasma, (3) a marked decrease in urine acidity with an increased elimination of phosphates, and (4) diuresis, for example, hyperpnea for 20 minutes may increase the urinary output from 56 c.c. per hour to 123 c.c. per hour and hyperpnea for 32 minutes may increase the urinary output approximately fivefold (from 46 c.c. to 220 c.c. per hour).<sup>3, 4, 5</sup>

It is evident that hyperventilation (carbon dioxide elimination) yields more free water with better secretion and better excretion.

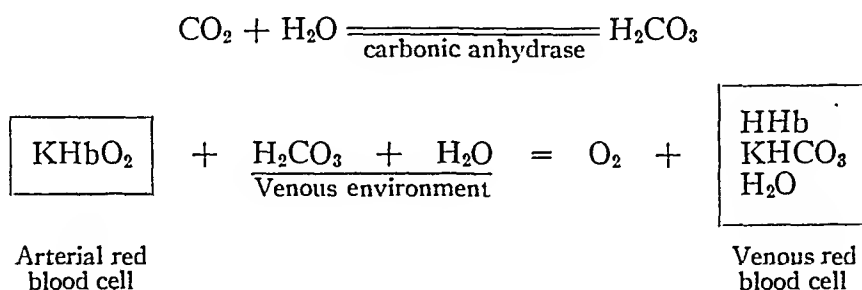
*Reduction of the Carbon Dioxide Combining Power of the Plasma (Alkali Reserve).* Agents, including hyperventilation, which produce a decrease in the carbon dioxide combining power of the plasma promote diuresis; ammonium chloride is such an agent. We have observed that the administration of 18 grams of ammonium chloride (12 capsules of 7.5 grains daily for three days) produced weight loss in 80 per cent of the 39 subjects studied, the average weight loss being 1.97 pounds per individual.<sup>5</sup>

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## THE EFFECT OF INCREASING CARBON DIOXIDE

*Red Blood Cells* absorb water from the plasma when carbon dioxide is passed through blood; this was demonstrated by Limbeck<sup>6</sup> as early as 1894 and it has been repeatedly confirmed. The red blood cells of the venous blood absorb carbon dioxide and water from their environment and as a result increase in size. The reaction may be expressed as follows:



*Increasing the Carbon Dioxide Combining Power of the Plasma (Alkali Reserve).* Increasing the carbon dioxide combining power of the plasma is accompanied by an increase in body water. We have noted<sup>5</sup> that the administration of 36 grams of sodium bicarbonate (4 grams t.i.d. for three days) produced a weight increase in 90 per cent of the 49 subjects studied; the average weight gain being 2.28 pounds per individual.

*Increase in Muscle Weight During Exercise.* Ranke (1865)<sup>7</sup> probably was the first to demonstrate that the stimulation of muscle was accompanied by an increased uptake of water. During the activity of skeletal muscle the muscle increases in weight and this is accompanied by a marked change in the distribution of water and electrolytes.<sup>8, 9, 10</sup> Carbon dioxide production is associated with the activity of skeletal muscle; therefore it is reasonable to consider that the accumulation of carbon dioxide might be a factor in the increased hydration of muscle during its activity.

## EXPERIMENTAL

The hydrophilic capacity of frog muscle was determined without, and with the presence of carbon dioxide, using: distilled water and graduated concentrations of the following: sodium chloride, ammonium chloride, hydrochloric acid, sodium hydroxide, glucose, urea, sodium bicarbonate, monobasic, and dibasic sodium phosphate.

Frog legs were sectioned at the hip joint, skinned, and the entire limb and foot were weighed, and placed in 100 c.c. of the test fluid contained in 150 c.c. beakers. The muscles were weighed again at the end of 4 hours and 20 hours. In some experiments the muscles were weighed each hour.

Table 1 is presented to show the hydration which occurred during 4 hours and 20 hours when the frog legs were immersed in distilled water. It will be observed that the fluid containing the muscles was subsequently

subjected to carbon dioxide for four hours; this was accomplished by placing the beakers on plate glass and covering them with a bell jar. The carbon dioxide was introduced through a side vent in the bell jar. The administration of carbon dioxide was accompanied by a decrease in the weight of

TABLE I

Solution Used	4 Hrs.	20 Hrs.	CO <sub>2</sub> 4 Hrs.
Triple Distilled H <sub>2</sub> O	+ 54	+ 69	- 13.8
Triple Distilled H <sub>2</sub> O	+ 58	+ 77	- 14.3
Triple Distilled H <sub>2</sub> O	+ 58	+ 84	- 14.
Triple Distilled H <sub>2</sub> O	+ 61	+ 72	- 12.
Triple Distilled H <sub>2</sub> O	+ 67	+ 83	- 16.
Triple Distilled H <sub>2</sub> O	+ 50	+ 171	- 12.

the hydrated muscles. The numbers recorded represent the per cent of gain or loss in terms of the original weight of the muscle.

An agent which causes dehydration of tissue has to exert its action in one of two ways: either by decreasing the hydrophilic capacity of the tissue or increasing the concentration of the solution surrounding the tissue. In order to test this conception, frog legs were immersed in distilled water and immediately placed in an atmosphere of carbon dioxide; chart 1 illustrates the results of this procedure. The muscles reached their maximum hydration in four hours and subsequently began losing water. It will be noted

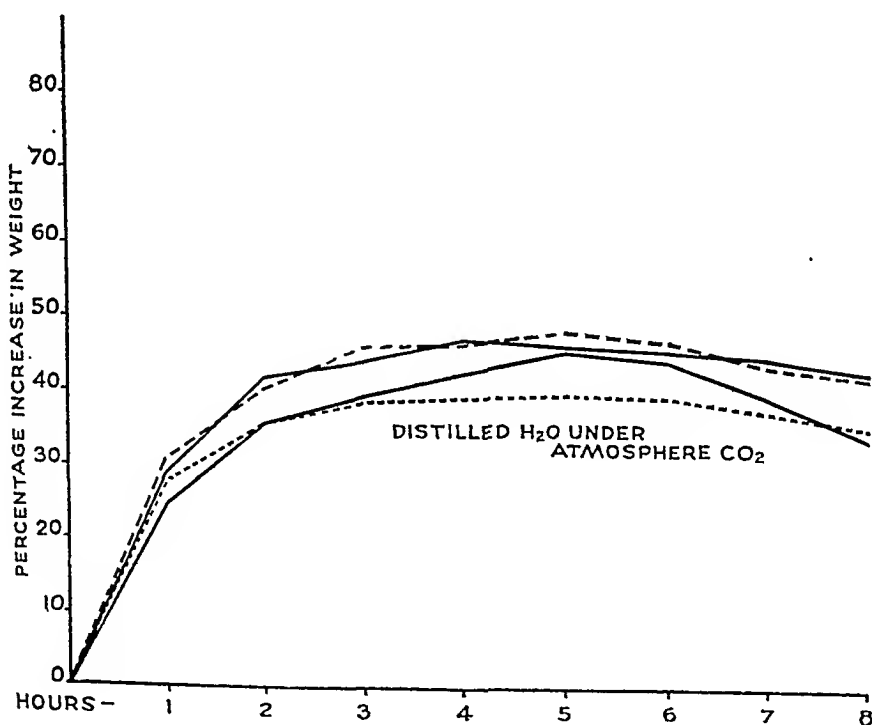


CHART 1.



that the hydration in the presence of carbon dioxide is much less than that occurring in untreated distilled water.

Since carbon dioxide exerted a dehydrating effect on hydrated muscle and also inhibited the hydration of muscle immersed in distilled water, we considered the possibility that this action might be due to the acid action of carbonic acid. Therefore, we next determined the effect of hydrochloric acid, and table 2 is a record of the results obtained with various concentra-

TABLE II

Solution Used	4 Hrs.	20 Hrs.	CO <sub>2</sub> 4 Hrs.
HCl N/10	+ 32	+ 49	+ 2.8
HCl N/20	+ 39	+ 65	+ 1.3
HCl N/40	+ 42	+ 59	- 4.2
HCl N/80	+ 60	+ 69	- 8.5
HCl N/160	+ 53	+ 59	- 16.

tions of hydrochloric acid. In only one respect are the results comparable with those obtained with carbon dioxide; the higher concentrations of hydrochloric acid, N/10-N/40, markedly retarded hydration during the first four hours. However, during the next 16 hours there was an increased hydration in such concentrations. At the end of 20 hours the solutions containing the muscles were subjected to an atmosphere of carbon dioxide with the result that the muscles in the more acid solutions continued to increase in weight, while those in the more dilute acid lost weight.

The results obtained with various concentrations of sodium hydroxide are presented in table 3; analysis of the data presents some interesting con-

TABLE III

Solution Used	4 Hrs.	20 Hrs.	CO <sub>2</sub> 4 Hrs.
NaOH N/10	+ 63	+ 81	- 8
NaOH N/20	+ 61	+ 82	- 13
NaOH N/40	+ 70	+ 81	- 15
NaOH N/80	+ 61	+ 77	- 11
NaOH N/160	+ 67	+ 78	- 9

trasts with those obtained from corresponding concentrations of hydrochloric acid. During the first four hours the degree of hydration was essentially the same in each of the concentrations of sodium hydroxide used; compared with hydrochloric acid the hydration was approximately double that obtained with the N/10 acid. At the end of 20 hours the total hydration in alkali was markedly greater than in acid, and when subjected to an atmosphere of carbon dioxide the muscles lost weight in all concentrations of sodium hydroxide.

The data we have presented reveal the fact that the addition of carbon dioxide to the fluid surrounding a hydrated muscle will cause dehydration of the muscle; also, if carbon dioxide is present throughout the experiment

the muscles swell less than in distilled water. The question arises: is this effect of carbon dioxide due to a decrease in the hydrophilic capacity of the muscle or is it due to the increase in ion concentration of the fluid surrounding the muscle? The fact that isosmotic solutions of urea are not isotonic prompted us to test the effect of urea. Chart 2 illustrates urea solutions

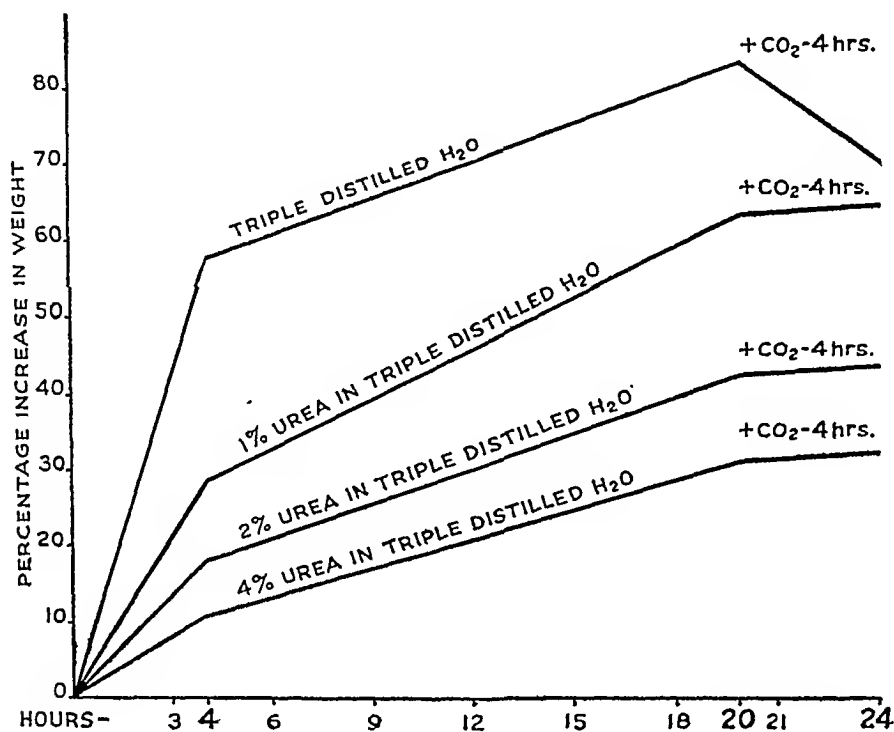


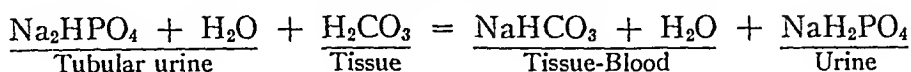
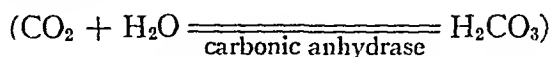
CHART 2.

without and with the presence of carbon dioxide. Since a 2 per cent urea solution is approximately isosmotic with mammalian physiological salt solution it is evident that urea does not establish an isotonic condition. It will be observed that the carbon dioxide atmosphere for four hours did not cause a fluid loss but instead a slight gain in weight was recorded, the gain being practically identical in all concentrations of urea.

### DEDUCTIONS

We have presented direct and indirect evidence to support the claim that absorption of water occurs in regions where carbon dioxide accumulates (venous blood) and secretion occurs in regions supplied by arterial blood, which is relatively low in carbon dioxide content. The kidney illustrates both secretion and absorption; the secretion occurring in the region supplied by arterial blood, and the absorption in the region of the venous supply. Normally carbon dioxide accumulates in the tissue and blood of the absorb-

ing area of the kidney and reacts with the tubular contents. The reaction may be expressed as follows:



In a previous discussion of this mechanism we have stated, "Normally the disodium phosphate does not pass through the kidney due to the fact that the sodium salt of such a weak acid dissociates and the free sodium ions combine with the carbon dioxide of the blood stream. During hyperventilation the carbon dioxide of the blood is depleted and allows the sodium to pass as the disodium phosphate, exerting a diuretic action."<sup>5</sup>

This interpretation of the reaction within the kidney is supported by Pitts.<sup>11</sup> The analysis of his experimental data on "The Renal Regulation of Acid Base Balance" prompted him to state: "Carbonic acid dissociates within the cell to form hydrogen ions and bicarbonate ions; the hydrogen ions are exchanged for sodium ions in the tubular lumen; and the sodium ions, accompanied by an equivalent number of bicarbonate ions are reabsorbed into the tubular blood." His studies were concerned with the mechanism for acidifying the urine and he did not consider water mobilization.

We are of the opinion that the accumulation of carbon dioxide in tissues produces an increased acidity which leads to the addition of base and the resulting combination becomes more hydrated. The direction in which the base and water move depends upon the degree of acid in the tissue cells, and the degree of alkali reserve of the blood in contact with the tissue. Increasing the alkali reserve affords more available base which diffuses from the higher to the lower concentration, increasing the hydration of the tissues. With decreased alkali reserve the base and water of the tissue cells tend to move toward the blood stream, decreasing the hydration of the tissues.

#### SOME RESPONSES WHICH ILLUSTRATE THE APPLICATION OF THE ABOVE INTERPRETATION

*Gaseous Exchange and Fluid Balance.* Armstrong<sup>12</sup> has shown that men subjected for four to seven hours daily to a simulated altitude of 12,000 feet in low-pressure chamber develop polyuria in which the urine output was increased 100 to 300 per cent above normal. More recently he states,<sup>13</sup> "the cause of the increase was not apparent."

The fluid balance of unanesthetized white rats in a low-pressure chamber responds to altitudes in a manner corresponding to human beings. The urine output at 10,000 feet altitude is not significantly different from the normal control figure, but at 15,000 feet altitude equivalent the urine in-

crease amounts to approximately 150 per cent and at 25,000 feet 300 per cent.<sup>14</sup>

Swann et al.<sup>15</sup> have also observed a negative water balance in rats during exposure to low barometric pressure. They concluded that anoxia was the main causative factor producing the negative water balance and based such a conclusion on the fact that the administration of oxygen prevented the phenomenon. They also observed that a mixture of 10.5 per cent oxygen and 89.5 nitrogen, maintained at the normal pressure of 760 mm. Hg, did not prevent the phenomenon.

The present author is of the opinion that the negative water balance, resulting from low barometric pressure, is due to the low oxygen content which stimulates respiration and thereby depletes the carbon dioxide of the body; the sequence of events is that previously outlined under hyperventilation diuresis. The respiratory response to increased altitude is stated by Armstrong,<sup>13</sup> as follows: "This varies in different individuals but it has been noted as low as 4,000 feet. At first, only the depth of breathing is increased which is an effective means of increasing the oxygen in the lungs since in shallow breathing very little fresh air gets past the dead air spaces. At about 12,000 feet altitude the increased depth in breathing amounts to between 20 and 100 per cent increase in lung ventilation."

*Blood Volume Response to Temperature Changes.* Animals exposed to low temperatures respond by shivering and increased muscle tone; this results in hemoconcentration and an increase in intracellular water. If the central nervous system becomes sufficiently chilled to cause general neuromuscular depression the movement of fluid is then in the opposite direction, and the result is subcutaneous edema and hydration of the blood.<sup>16, 17</sup> It is evident that temperature changes, with accompanying changes in metabolic activity, can alter the hematocrit and blood cell count.

*Posture and Fluid Mobilization.* Numerous investigators have demonstrated changes in plasma volume resulting from postural changes and exercise.<sup>18, 19, 20, 21, 22</sup> A diurnal fluctuation of 10 to 15 per cent in serum protein, dependent upon postural factors, has been shown to occur regularly in individuals during normal existence.<sup>23</sup> This fluctuation is doubtlessly related to the alkaline tide and probably finds its explanation in the observations of Leathes.<sup>3</sup> He focused his attention on the part played by respiration in the production of the morning alkaline tide. While his chief interest was in the reaction of the urine accompanying the hyperventilation on awakening, his data also show a marked increase in urine production. It should be kept in mind that an individual at bed rest with complete muscle relaxation may normally have a plasma volume above the accepted normal, and a serum protein concentration below the accepted normal.

## CONCLUSION

Gaseous exchange plays a part in the mobilization of body fluid.

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# PRESCRIPTION OF PHYSICAL MEDICINE BY THE INTERNIST \*

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ADEQUATE and successful use of physical agents can be expected only when they are prescribed in a thoughtful and scientific manner. It is the duty, therefore, of physicians prescribing physical medicine to use similar accuracy and detail as when prescribing drugs. In both instances instructions are given to an intermediary highly skilled in technical matters, but untrained in diagnosis. Full advantage of the physical therapist's technical skill can be obtained only by indicating the nature of the condition to be treated and the specific effects to be expected from therapy. The choice of agents to be used should be determined by the physician and an intelligent selection can be achieved solely through knowledge of the actions of the various physical therapeutic measures. As a background for prescription writing it is therefore in order to consider briefly some of the known effects of physical agents on various tissues of the body. As physical agents act primarily from the exterior, it is logical to consider first their effect on the superficial structures.

## SKIN

Most forms of physical therapy have some effect upon the skin, and we will accordingly discuss some of the primary changes which can be evoked.

*Temperature Increase.* In considering methods of increasing the temperature of the skin it is well to review the elementary physics involved. The most familiar means of heating is by conduction. In this situation one envisions an exchange of molecular energy from the hotter object to the cooler which is achieved only by contact. This method of heating is known to be relatively slow and consequently any important change in temperature can be achieved only by proper allowance for time. Our most familiar home heating devices are examples of conductive heating. These are the use of the hot water bottle, electric pad, warm water soaks or immersion in melted paraffin wax. In all such methods of heating the temperature of the heating agent must remain within safe levels, not exceeding 110 to 113° F., and as a general rule 30-minute applications are the minimum necessary for an adequate temperature increase of the area. Water is very advantageously used for heating because of its high specific heat, but more prolonged hyperemia can be obtained by melted paraffin. Electric pads avoid the difficulties of cooling but are less flexible in application and are not free of hazard from burn and shock.

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Another less familiar form of heating is by convection. By this we mean movement of warm currents of air or liquids. Although some hot air heating devices have been designed, these are so infrequently used that they warrant no detailed discussion. The penetration of heat to deeper tissues is again the same slow process as with conductive heating.

Increasing temperature by the use of radiant energy involves consideration of the factors of penetration and absorption of different wave lengths. As an increase in temperature is dependent on absorption of radiant energy, when the skin itself is the structure to be primarily heated, those wave lengths of radiant energy should be selected which are known to be absorbed by the skin. For this purpose infra-red generators should be used which emit primarily in the far infra-red range with a wave length greater than 1500 millimicrons. These invisible infra-red rays are absorbed completely by the skin and consequently cannot be considered as penetrating in spite of suggestive advertising to the contrary. Any depth heating effect is by the slow process of conduction from the warmed skin surfaces to the deeper layers of subcutaneous tissue. When heating is desired at a greater depth, it is more efficient to use the near infra-red rays from a luminous heat source, as a portion of this energy is transmitted through the skin to the subcutaneous levels where it is absorbed, so that penetration is more efficient and quick.

A fourth method of heating is by the conversion of high frequency electrical currents to heat, particularly the use of short wave diathermy. Even though these high frequency electrical currents can penetrate tissues to great depths, in the presence of normal circulation the skin is always heated at the same rate as the deep tissues and, in fact, the greatest heating effect occurs superficially which is desirable, as we rely on sensation of skin temperature to adjust dosage.

*Sedative Effects.* One of the commonest indications for the use of physical agents is for the relief of pain. Although the origin of the pain is only occasionally situated in the skin, the counter-irritant action of certain measures may have a sedative effect on deep seated pain. Experimental studies have shown that increase of skin temperature by one of the methods already mentioned is of some value in relieving pain from inflammatory processes in the skin. Cold also has a sedative action, but the alternate use of heat and cold has been found to be more efficient.<sup>1</sup> Another measure of known value as a counterirritant is histamine iontophoresis. In some cases an erythema produced by ultraviolet irradiation may relieve the pain of herpes zoster, although the mechanism is obscure. The pruritus of various skin conditions is also lessened occasionally by ultraviolet irradiation, but it must be used with caution as many acute processes are made worse.

*Bactericidal Effects.* The shorter wave lengths of ultraviolet radiation are known to have definite power to kill bacteria in the air and to a limited extent on surfaces. Experience has shown, however, that effective sterilization of skin for surgical purposes cannot be achieved safely with ultra-

violet irradiation. Any beneficial effects on pathogenic organisms in wounds or chronic ulcers are probably achieved secondarily through a stimulating effect on the tissues rather than by direct action on the bacteria. There is only limited experimental work available on the effect of radiant energy in wound healing. Clinical experience suggests that infra-red radiation alone or together with mild ultraviolet erythema production occasionally stimulates sluggish tissues in overcoming chronic infection and consequently hastens epithelial growth. The value of general ultraviolet irradiation for increasing general body resistance to infection is still controversial. Most controlled series of studies have dealt with the problem of the common cold and there is no conclusive value described, although some reports suggest a beneficial effect.<sup>2, 3</sup>

*Pigmentation.* Patients are frequently referred to physical therapy departments in order to acquire a so-called sun tan, but the patient more often than the physician is convinced of the desirability of such pigmentation. Mottled pigmentation can be produced by prolonged over-exposure to heat in any form and frequently follows home treatment. The even pigmentation following normal sunburn is produced in the skin in response to stimulation from ultraviolet radiation particularly of the longer wave lengths.<sup>4</sup>

Mercury, quartz, ultraviolet generators, although efficient in producing erythema, are not as effective in tanning as carbon arc or natural sunlight. Although there is little scientific proof of the value of general ultraviolet irradiation except in certain skin conditions, there can be no doubt of the frequent feeling of well-being associated with the appearance of ruddy health which comes from a good coat of tan, and the physician may wisely at times take advantage of this for psychological purposes alone. The actual prescription of ultraviolet should be in terms of the degree of erythema desired rather than in details of lamp distance and duration of exposure, unless the physician is familiar with the erythema capacity of the lamp to be used. Any properly trained technician can correctly adjust the exposure necessary to produce the result desired by the physician. Serious burns can result from prescriptions of ultraviolet given in terms of exposure time based on a lamp the doctor is familiar with, while the lamp the technician uses may be many times more powerful. I have frequently received prescription for three-minute exposures when the physician desired only an erythema dose, whereas such an exposure with our lamp would be twelve times the minimal erythema dose. Until an inexpensive and generally used meter is available, the erythema dose still remains the unit of measurement for ultraviolet radiation.

*Circulation Increase.* Most of the agents already mentioned serve to produce an increase in skin circulation as well as of the deeper tissues. It is well known that increase in temperature results in an opening of capillary beds, a more rapid arterial and venous flow, and in addition increased lymphatic drainage. Hyperemia is also produced by ultraviolet erythema and by iontophoresis. Massage too is capable of producing definite circulatory changes in the skin, even superficial stroking serving to open capil-



laries and more heavy stroking and friction producing a fairly prolonged hyperemia. It is probable that a large proportion of the beneficial effects of physical agents can be ascribed to the resultant increase in circulation.

## MUSCLE

*Temperature Elevation.* The physical factors already mentioned in regard to heating the skin apply to increasing the temperature of muscles. The simplest method of heating is, of course, by conduction but, as already shown, this method is necessarily slow. It is more effective to have energy transmitted through the skin so that the heating effect may be relatively greater in the deeper tissues. Consequently the near infra-red from luminous heat sources is preferable to far infra-red generators. High frequency currents of diathermy have been shown to be the most efficient method of heating at a depth and should be used when this is desired.

*Relaxation of Spasm.* Muscle spasm is undesirable because of the resultant pain and the immobilization of joints which may lead to contracture. The mechanism of production of muscle spasm is not altogether clear, although one envisions a reflex arc through the spinal cord. If one accepts this explanation, it is reasonable to hypothesize reduction of spasm by the influence of heat with its known sedative effect upon sensory nerve endings, and clinical experience has shown this to be true. When very skilfully given, it is also possible to relax muscle spasm by massage, but the actual technic is so much an individual art that it is wisest to advise the technician to give massage for sedative effect and relief of muscle spasm rather than to indicate the details of technic. Muscle spasm can also be prevented or diminished by carefully guided active assisted exercises and by traction. Relaxation therapy may include special technics such as deep breathing and psychosuggestion. The spasticity from upper motor neurone disease, including the rigidity of Parkinson's disease, may be diminished by rhythmical exercises and special muscle reëducation technics. Occupational therapy is often prescribed to advantage in these cases.

*Strengthening.* Muscles with intact nerve supply can be strengthened only by active exercises graded in their resistance to produce some fatigue and consequent hypertrophy. In general, the therapist is more familiar with the specific exercises than the physician prescribing treatment, and it is sufficient in the prescription to indicate graded exercises for strengthening effect with precaution as necessary for range of motion and general limitations such as indicated by poor cardiac reserve.

Prevention of excessive atrophy following denervation can be achieved best by appropriate electrical stimulation. Although actual nerve regeneration cannot be changed by electrical stimulation, there is now a considerable body of experimental evidence to show that interrupted direct current stimulation of a frequency sufficient to cause tetanic contraction of the denervated muscle, repeated daily or even less often, enhances the speed of recovery once reinnervation occurs.

*Stretching.* One of the most frequent problems in the field of physical medicine is overcoming contractures of soft tissues including muscle. In most instances this is best achieved by active exercises under control of the patient rather than by passive stretching. Frequently mechanical devices and leverage effects are used, always under active muscle control. In the prescription it is usually adequate to order active stretching or very gentle passive stretching with the instruction that no pain, or only minimal pain, is to be produced. Further details may include suggestions as to the use of weights, pulleys, elastic traction, etc. Stretching is usually best achieved by the synergistic action of several agents, including heat, sedative massage, and finally exercises. Frequently optimum results are observed during immersion in warm water and with the mild massaging effect of whirlpool agitation. In this case the exercises are given simultaneously with the heat and massage.

*Bones.* The effect of physical agents on the metabolism of bones is only sketchily understood. The action of ultraviolet irradiation in the prevention of rickets is well known and needs no further discussion here. It is also generally conceded that oral use of vitamin D precludes the necessity of ultraviolet irradiation. The internist should remember, however, that in cases of impaired intestinal absorption calcium metabolism may be improved and tetany relieved by general irradiation with ultraviolet when oral medications are unsuccessful. That bone atrophy results from immobilization is well known and it is generally accepted, without the necessity of laboratory proof, that exercise is beneficial in preventing excessive atrophy in these instances. The exact rôle of deep heating particularly by diathermy in cases of fracture and delayed union still awaits more experimental investigation. The value of physical therapy in fractures cannot be overlooked, but it is of more interest to the surgeon than the internist.

*Joints.* Physical therapy and, in many cases, occupational therapy play an important rôle in the total treatment program of joint disease. As joints require motion for the maintenance of normal physiologic action, in the presence of inflammation and pain the proper amount of motion can best be obtained under the guidance of a trained physical therapist. It is usually essential to diminish pain and muscle spasm and this can be effectively accomplished in the majority of cases by judicious use of local heat, occasionally gentle, sedative massage, and guided active assisted exercises within a pain-free range. In the presence of pain associated with inflammatory joint disease, muscle atrophy and loss of normal control of movement are frequent findings. Such patients are benefited by skilled supervision in muscle re-education to prevent atrophy and to increase the strength which is necessary for maintenance of joint function. Active exercises are the rule in joint disease. Passive motion should be reserved for individual cases as selected by the specialist. There is no conclusive experimental evidence that heat of any sort, iontophoresis, ultraviolet irradiation, massage, or exercise has any specific effect on joint function except that which can be explained by

motion. There is a possible exception in that removal of effusion in joints can be speeded by massage and exercise, possibly also by deep heat. There is no evidence that inflammatory processes can be cured by these methods. Further details of prescription in the case of joint disease will be referred to later.

*Intestines.* Heat is frequently applied to the abdomen for pain of intestinal origin. There is evidence to support the belief that such applications diminish increased intestinal motility.<sup>5</sup> Although cold applied externally may be thought to diminish intestinal activity, experimental evidence suggests the opposite effect.<sup>5</sup> Symptomatic benefits of local heat in cases of intestinal pain should not be overlooked. Pain arising from other viscera, particularly the pelvic organs, may be reduced by deep heat as applied by means of short wave diathermy. These effects are probably produced by the increase in circulation secondary to changes in temperature gradients.

*Metabolism.* There are only a few recognized metabolic effects ascribed to the use of physical agents. The effect on calcium and phosphorus metabolism in the prevention of rickets in children by ultraviolet irradiation is outstanding. Systemic application of heat also generally increases oxidative processes. Exercise, too, increases heat production and may secondarily improve metabolism in various portions of the body. The effect of ultraviolet on metabolism, particularly immunological responses, is still to be determined by further investigation.

*Peripheral Circulation.* It has already been shown that the normal response to an increase in temperature of the skin and subcutaneous tissues is an increase in circulation. This involves dilatation of the capillary bed, increased rate of arterial blood flow, and improvement in venous and lymphatic return. Superficial capillary dilatation can also be achieved by massage and iontophoresis. Venous and lymphatic flow is improved by fairly heavy massage and, in addition, active muscle contraction. It should be remembered that this increase in circulation from the application of heat is due to reflex activity. When using high frequency electrical currents, generalized vascular responses are obtained if high dosage is used at the beginning of the application. This immediately increases the circulatory rate and dissipates the heating effect. Moderate dosage is accordingly advisable at the beginning of the application and only later increasing the total amount of electrical energy. It is also possible through reflex activity to increase the rate of blood flow in the extremities by the application of heat to distant parts such as the trunk or upper extremities. This method of relaxing vasospasm is safer in patients with impaired circulation where the increased metabolism resulting from direct application of heat may be dangerous.

The use of alternate hot and cold applications in cases of vasospasm is now generally recognized to be of little value, if not contraindicated. The use of mechanical suction and pressure apparatus is also thought to be of very limited usefulness in the majority of individuals with peripheral vas-

cular disease. Buerger exercises, although commonly prescribed and certainly not harmful, are, however, not of proved worth scientifically. They may still be used empirically and also the oscillating bed in selected cases for the same purpose.

*Nerves.* There is a large body of clinical evidence to indicate that painful impulses can be diminished by the application of heat to the surface. A few experiments have shown that heat and cold, or alternate use of both, have a definite sedative effect as well as other counter-irritant measures.<sup>1</sup>

The spasticity of muscles resulting from upper motor neurone disease as already mentioned can be favorably influenced by the use of heat, carefully used sedative massage, followed by a skilfully controlled exercise and training program.

In the case of supposed diminished activity of the neuro-muscular apparatus, massage is known to stimulate so that improved muscle tone results. Such massage can be used with advantage in cases of prolonged bed rest prior to mobilization. The stimulating effect of gentle massage in certain cases of psychiatric disorders is well recognized clinically, although the mechanism of its action is obscure. Hydrotherapeutic measures in psychiatric conditions are also accepted forms of treatment, but beyond the scope of this presentation.

### DIAGNOSIS

Having discussed briefly the scientific background of physical medicine, we may now proceed with some of the indications for its use and details of the prescription. Although with other forms of treatment it is generally conceded that diagnosis must be made before beneficial treatment can be anticipated, it is still commonly the practice to send patients with undiagnosed symptoms to physical therapy. If a physician in the field is consulted, it is then up to him to make the diagnosis and prescribe the treatment in detail. Otherwise the technician is too often left in the unfortunate position of having to decide the details of treatment for symptoms of unknown etiology. For the best results it is obvious that a working diagnosis should be provided in order that the physical therapy prescription may be intelligently utilized. There are frequent occasions, however, when response to physical therapeutic measures may aid in arriving at the ultimate diagnosis. This is a stimulating situation for the specialist in physical medicine and a diagnostic tool not to be overlooked by the internist. For example, the differential diagnosis of ruptured intervertebral disc, rheumatoid arthritis, and peripheral neuritis may frequently be made more clear by the response to physical therapy. Similarly, symptoms of mechanical origin in relation to the spinal column may be improved by remedial exercises, thus differentiating them from infectious processes. More specific instances of diagnostic methods in physical medicine have to do with electrical testing of nerves and muscles.

## CHOICE OF PHYSICAL THERAPEUTIC AGENTS

After arriving at an understanding of the disturbed physiologic processes leading to symptoms in a given case and imparting this information to the physical therapist as a part of the prescription, the next problem is the choice of agents to be used. Instead of a routine order of baking and massage, with even a minimal background of information concerning the effects of physical agents as outlined, it is the duty of the physician to decide if increased temperature is desirable and, if so, either indicate which tissues should receive the increased heat or indicate the method of heating most suitable for this effect. Heat may occasionally be contraindicated or of no benefit and, if so, should be omitted from the prescription. The specific values of massage, for stimulation and also for sedative effects, should be kept in mind and the prescription should mention the effect desired when prescribing massage. When exercises are prescribed, it is best to indicate the result expected rather than mention simply active or passive exercises. If relaxation of spastic reflexes or muscle spasm is wished, exercises with that in view should be suggested and likewise exercises for strengthening, stretching, or improvement in muscle control, coördination, and balance. Further details of exercises can safely be left in the hands of a well trained technician by simply mentioning the precautions of pain, fatigue, etc. The duration of application of each agent, with the exception of ultraviolet irradiation, can be indicated within reasonable limits depending on the tolerance of the patient and reaction to treatment. Synergistic effects of a combination of measures should not be overlooked: passive means of increasing circulation by heat and massage can with advantage precede active measures such as exercise so that the total response is greater than the individual application of the agents separately.

The frequency of treatment is a matter of individual decision and includes evaluation of a variety of social, economic, and psychological factors as well as physiologic effects. When passive measures alone are used they must be repeated frequently, at least daily or more often. Treatment and supervision may be less frequent in cases where the patient can be instructed to participate at home in the use of heat, occasionally massage, and always in active exercises. It is always of importance to determine when the time has come to stop treatment. This can be done only by a proper evaluation of the effects, frequent examination by the therapist with adequate progress notes, and measurements by the physician. Every objective means possible should be employed for the purpose of evaluating the effect of treatment and determining when progress is no longer being achieved. The aid of occupational therapy should not be overlooked in encouraging the patient to acquire a more satisfactory adjustment to his disease and the treatment. In the presence of impairment of extremity function, it is prescribed for its remedial effect. It is frequently possible to accomplish more by skilfully guided crafts and shop work than by specified exercises. A well rounded

program of therapy includes proper coördination between physical and occupational therapy and gradation finally to occupational therapy alone as the last step toward free, unsupervised activity.

### INDICATIONS FOR PHYSICAL MEDICINE

*Joint Disease.* Now that the general features of proper prescription of physical medicine have been discussed, we will mention briefly some of the definite indications for the use of physical and occupational therapy in medical conditions. Rheumatoid arthritis is an outstanding example of a medical condition in which physical measures are of value. In the patient confined to bed, training in body mechanics is essential, including recumbent postural exercises with progression to increased activity in the sitting and standing positions, with emphasis on proper mechanics in walking. To improve individual joint function a combination of physical measures is indicated, including thermotherapy, massage, splintage, and exercise. The choice of heat to increase local circulation is dependent somewhat on facilities available and frequent short applications are more desirable than occasional more prolonged and complicated measures. Efficiently applied, hot fomentations of 20 to 30 minutes three or four times daily, followed by an exercise period, are extremely useful. In some patients warm whirlpool baths or complete immersion in warm water make possible greater facility in exercise. Therapeutic pools may occasionally be utilized to advantage in teaching arthritic patients to walk. In general, a well organized exercise program is the single agent of utmost importance. Every patient should be taught correct methods of exercising involved joints so that damage is not done and all possible joint range maintained together with adequate muscle strength. All but the most severely crippled patients can be taught with proper supervision how to exercise their joints three to four times daily, with supervision only several times a week. In this disease which so frequently is chronic, more elaborate means of treatment are generally not indicated, for frequently repeated simple measures which can be used in the home are more desirable. The physical therapy program should be properly integrated with general medical care and orthopedic supervision. The intensity of measures, particularly exercise, should be regulated according to the general condition of the patient as suggested by symptoms, laboratory tests, and degree of muscle spasm. Mechanical aids should not be overlooked such as pulley apparatus, stationary bicycles, bed roller skates, and traction. Occupational therapy for psychological and functional effects should be included in the overall program of treatment. Frequently the occupational therapist may be of service in evaluation and pre-vocational training.

Physical therapy is also of definite value in the treatment of degenerative joint disease. Acute symptoms may be relieved by rest, local applications of heat, and gentle sedative massage. With subsidence of acute symptoms,

emphasis is then placed on strengthening of supporting musculature by carefully graded exercises. Whenever possible, postural defects should be remedied by stretching of slightly contracted soft tissues responsible for faulty posture and strengthening of improperly used and flabby musculature.

Physical therapy is especially recommended in cases of pain localized to periarticular structures, particularly individual muscles in the back, shoulder girdle, and neck areas. In these conditions, often called fibrositis, heavy massage including friction followed by light sedative massage, local use of heat, and corrective exercises may produce dramatic relief of symptoms.

The rôle of physical therapy in the treatment of infectious arthritis is secondary to specific measures when available. In those cases responding to chemotherapy, aside from the occasional use of heat for relief of pain, physical therapy is postponed until the infectious process is controlled. Mobilization may then be instigated with the aid of gentle massage and active guided exercises. In tuberculous arthritis the emphasis is, of course, on healing the process as a whole rather than an attempt to preserve individual joint function, so that heat, massage, and exercise are contraindicated. Carefully graded exposure to the sun according to standard technics, or general artificial ultraviolet irradiation, is used to improve general resistance. The occasional case of gonorrheal arthritis which is resistant to chemotherapy may be aided by artificial fever therapy in the fever cabinet. Such treatment is a highly specialized procedure, requiring expert technical skill and experience. It is to be undertaken only in hospitalized patients and by an experienced fever treatment staff.

There remain the large number of patients with symptoms referable to joints and supporting musculature, particularly in the region of the shoulder, back, and feet. In patients complaining of pain in the shoulder region, particularly when a localized area of tenderness is present, the diagnosis of bursitis is frequently made and physical therapy ordered. Perhaps the commonest prescription is for diathermy, either short wave technic or conventional long wave diathermy, the treatment averaging 30 to 40 minutes and repeated daily or on alternate days. Many cases of acute bursitis, however, do not respond favorably to diathermy, the stimulation to circulation apparently causing an increase in pain. These patients get more symptomatic relief from application of cold locally or a more superficial type of heating as with infra-red or luminous heat. Massage to the points of tenderness is usually contraindicated, although gentle sedative massage to surrounding muscles in spasm may be beneficial. Rest is of more importance than exercise in the early cases, but it is important to maintain a full range of motion by carefully guided active or active assisted exercises through the full range at least once daily. In cases of chronic adhesive bursitis, active and passive stretching may be added to the treatment prescription as soon as pain tolerance will allow. As the period of disability in these cases is long, it is wise to forewarn patients of this fact in order that they may persist in treatment. Physical therapy is often successfully combined with other

measures including irrigation with novocaine and saline, exploration and surgical removal of calcium deposits when present, or following manipulation for freeing of adhesions. In the shoulder where limitation of motion is so frequent after prolonged immobilization of muscle spasm, it is always wise to secure as much freedom from pain as possible by use of non-habit forming analgesics, particularly salicylates, in order that the patient may be able to perform exercises.

The problem of diagnosis and treatment of back pain is too complex to be discussed in any detail in this presentation. In the majority of cases a period of conservative treatment consisting in rest in bed with proper support to the back, analgesics and local use of heat for relief of pain, and sedative massage, when tolerated, is justifiable. Simple cases of mechanical back strain will respond to such treatment; probably also certain early cases of rheumatoid arthritis, and possibly some cases of protruding intervertebral disc. Pain having been relieved, the patient may then be gradually mobilized first with recumbent exercises for the low back, abdominal musculature and lower extremities; followed by posture instruction in the upright position and proper mechanical use of the back. Diathermy is a popular method of heating in these cases, probably with some justification because of the large amount of tissue to be heated in the back area.

*Diseases of Blood-Forming Organs.* Ultraviolet rays have been reported as favorably influencing some types of anemia. This effect is limited, non-specific, and far less efficient than dietetic therapy and hematopoietic agents. Subacute combined degeneration of the spinal cord is a complication of pernicious anemia that often requires prolonged periods of muscle reëducation in addition to adequate replacement therapy during rehabilitation.

*Endocrine and Metabolic Disorders.* In a limited number of cases physical therapy is of value in diseases of the endocrine glands and in disorders of metabolism. In gout, because of its interference with joint function, some symptomatic relief may be obtained by physical means. Pain may be diminished by use of hot compresses and in some cases with cold applications and rest. During convalescence mild heat and graduated exercises aid in mobilizing the patient.

Exercise is known to improve sugar tolerance of diabetic patients when participated in to the proper degree. In the event of diabetic neuritis relief of pain is often achieved by careful administration of heat. In the event of pronounced muscular weakness, muscle reëducation in the form of specific strengthening exercises may be indicated.

Obese patients are frequently referred to physical therapy departments for weight reduction. Passive procedures, such as massage or vibration, however, are valueless. Heat treatments, such as cabinet baths or steam baths, temporarily reduce weight through dehydration but are not of permanent value. Caloric requirements may be increased by prescribed exercises but are successful only in combination with strict dietary control.

*Pulmonary Disease.* Although short wave diathermy has been used as an adjunct in the treatment of pneumonia and bronchitis particularly for



relief of pain, it is very rarely needed. Many patients with bronchial asthma are benefited by special breathing exercises. Postural exercises are indicated in the prevention and treatment of scoliosis secondary to lung abscesses, empyema, and thoracoplasty. In pulmonary tuberculosis heliotherapy is rarely indicated, although of benefit in extra-pulmonary complications such as involvement of bones, joints and the larynx. Graded convalescent exercises and occupational therapy have a definite place in rehabilitation of patients with tuberculosis.

*Gastrointestinal Disease.* Patients confined to bed for considerable periods of time because of peptic ulcer, ulcerative colitis, or other disorders of the gastrointestinal tract may be helped in their adjustment to the disease and hospitalization by diversional occupational therapy. Where psychological or emotional factors are important, the occupational therapist may be guided specifically by the psychiatrist interested in the patient. Physical therapy is not often needed, but pain from hypermotility of the intestinal tract may be diminished through the application of luminous heat or diathermy to the abdominal wall. Debilitated patients often respond with satisfaction to stimulating doses of general ultraviolet irradiation. Convalescent bed exercises may also speed recovery.

*Heart Disease.* The rehabilitation of many cardiac patients may be facilitated by suitable physical and occupational therapy. This consists in light gentle massage, followed by graded exercises or games and activities in the form of occupational therapy.

These are only a few of the conditions benefited by including physical medicine in the treatment regimen selected as illustrative examples.

### SUMMARY

In conclusion I should again like to emphasize the importance of the prescription in physical medicine. An adequate prescription should include: (1) a working diagnosis; (2) specific instructions as to choice of agents; (3) indication of effects to be produced; (4) statement of duration and frequency of treatment.

Such a prescription can be written by the internist with some knowledge of the scientific basis of physical medicine.

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# BRONCHOPULMONARY ACTINOMYCOSIS \*

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THE presence of actinomyces in chronic bronchopulmonary infections is more common than it is generally considered to be. Interest in this subject was stimulated following isolation of the ray fungus in two patients with pulmonary suppuration. These patients required pulmonary resection in combination with chemotherapy to obtain cures.<sup>1</sup> Since then careful search for this organism has been made in similar patients. During the six-month period from May to November 1945, 240 patients were treated for chronic bronchopulmonary infections. Of these, 109 patients had *Actinomyces israeli* isolated (by direct examination and culture) from the sputum, and 65 from bronchoscopic specimens. The exudate aspirated from lung abscesses in six patients, and the drainage from sinus tracts in two patients with empyemas secondary to pulmonary suppuration were also found to contain actinomyces in combination with other organisms.

The 65 patients from whom actinomyces were cultured from bronchoscopic specimens included 37 with varying degrees of bronchiectasis and pneumonitis, eight with lung abscesses, five with pulmonary suppuration, five with aspiration pneumonia, and two with pulmonary suppuration distal to obstructing carcinomas. In eight additional patients the only apparent disease was chronic bronchitis. In no case was *Actinomyces israeli* found to the exclusion of other organisms. In a number of patients this fungus appeared to predominate, but usually other organisms such as streptococci, staphylococci, spirochetes and fusiform bacilli and other less common organisms, were also isolated.

It has been known for years that *Actinomyces bovis (israeli)* may be an inhabitant of the normal mouth. It has not been generally appreciated that this same organism may also be frequently found in bronchopulmonary infections. The source of such infections is undoubtedly the result of aspiration of mouth and pharyngeal exudates. The ciliary and peristaltic cleansing action of the normal bronchi in healthy individuals prevents such aspirated flora from assuming any clinical significance. When this physiological action is lost in patients with bronchopulmonary diseases such as bronchiectasis, the presence of mouth organisms deep in exudates can readily be explained. Actinomyces in infections such as pulmonary suppuration, chronic lung abscesses, and chronic pneumonitis result also from aspiration. In most instances they are of no clinical importance until anaerobic conditions occur. A blocked bronchus secondary to a plug of exudate would initiate such anaerobic conditions.

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The finding of actinomyces with such frequency originally caused considerable concern. Previous experience had related only to isolated cases. Was this an extraordinarily large series of bronchopulmonary actinomycosis, or should such patients be considered as cases of bronchopulmonary infection in which actinomyces, as well as other organisms, were isolated after careful bacteriological examinations? On what basis should pulmonary actinomycosis as a clinical entity be differentiated from pulmonary suppuration in which the ray fungus was only one of several organisms present?

It might be assumed that the term "pulmonary actinomycosis" should be applied only to those patients who have pulmonary suppuration associated with chest wall sinuses from which this organism can be isolated. However, it is known that pyogenic, as well as tuberculous infections, may also have draining sinuses secondary to underlying pleural and pulmonary involvement. The term "pulmonary actinomycosis" is then comparable to the terms "streptococcal," "staphylococcal," and "spirochetal" pneumonitis. There is no question that actinomyces under certain conditions may predispose to chronicity and as such may be partially responsible for the development of chronicity in bronchopulmonary infections.

Care was exercised to verify the identity of this supposedly pathogenic non acid-fast anaerobic ray fungus. With accumulated experience, it became apparent that the presence of actinomyces in bronchial and pulmonary exudates was a rather common occurrence and was not so significant clinically as had been originally thought. The clinical course and response to chemotherapeutic or surgical measures of patients with pulmonary suppuration did not appear to be influenced by the presence or absence of actinomyces. As is well known, pulmonary suppuration is a very chronic condition in itself.

At first additional precautions were followed when actinomyces were present. Increased dosages of sulfonamides and penicillin were employed preoperatively, if operations were to be performed, but this was later found to be unnecessary. Considerable discussion arose as to the advisability of performing operative procedures in the presence of actinomyces for fear of spreading the infection and the development of sinuses. Should a patient with actinomycotic pulmonary suppuration be continued on chemotherapeutic management instead of having operative therapy even though there had been no improvement? Would a chronic draining sinus follow drainage of an actinomycotic lung abscess, or would an actinomycotic empyema follow a lobectomy? The treatment of these patients, however, was not modified because of the presence of actinomyces. Operations were performed when indicated and in no instance was the post-operative course complicated by actinomycotic empyemas or draining sinuses. Actinomyces were isolated in the pleural fluid of one patient following pneumonectomy. The fluid promptly became sterile, however, with intrapleural injections of penicillin and sulfadiazine.

It is now felt that the presence of this organism is much less a factor

in the determination of the clinical course, chronicity, and prognosis of such infections than the mechanical factors of bronchial occlusion or drainage, tissue destruction, fibrosis, and avascularity. Patients with chronic bronchiopulmonary infections in which these mechanical factors were present were just as resistant to conservative therapy as were those complicated by actinomyces.

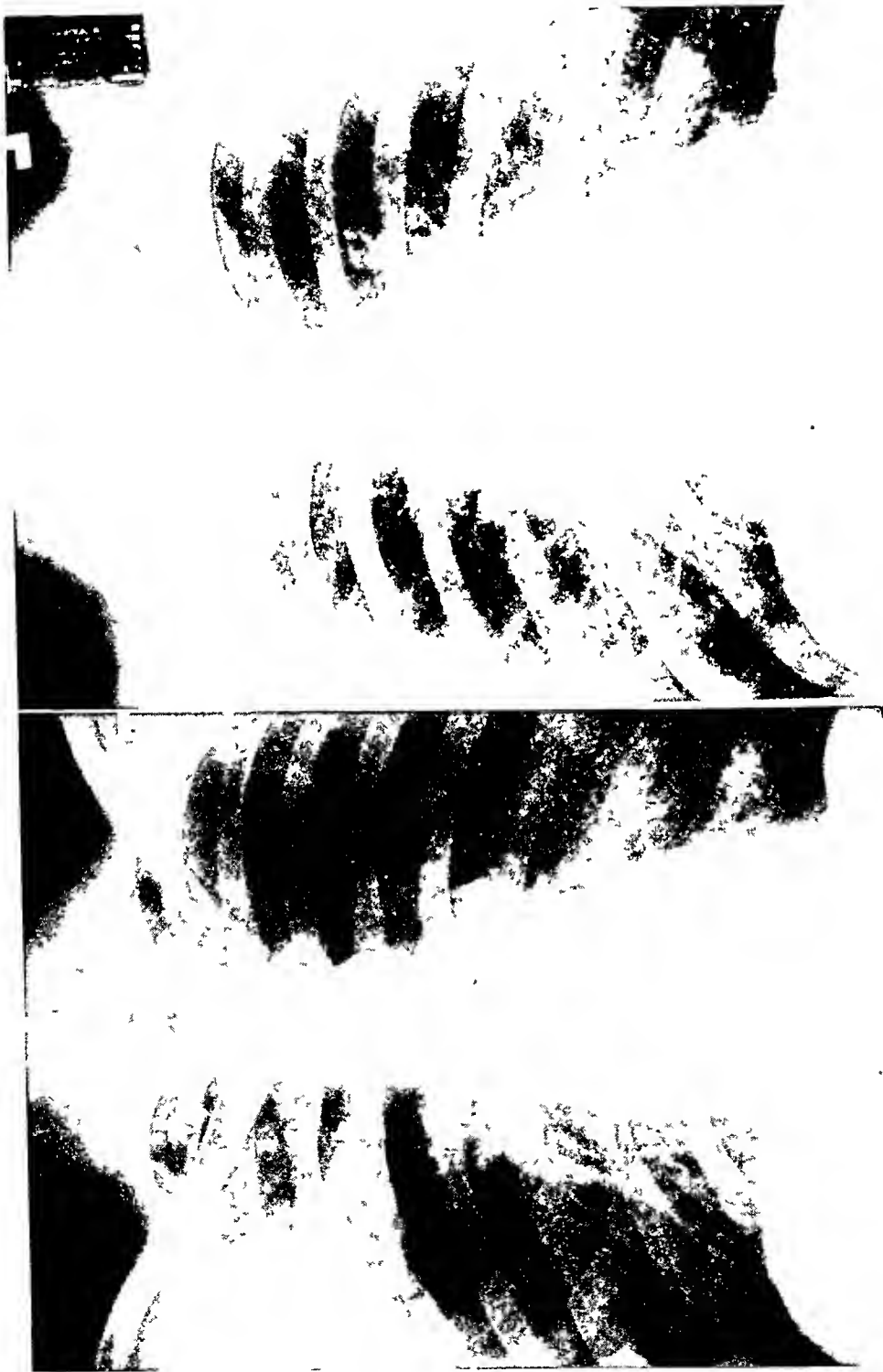
Approximately 50 per cent of the patients with bronchiectasis had actinomyces isolated bronchoscopically. There was nothing characteristic about this group except that the sputum appeared to be more copious in amount, more foul in odor, and more frequently bloody than when actinomyces were not present. The high incidence of bloody sputum probably results from the vascular granulation tissue seen in actinomycosis.

The patients with minimal bronchiectasis, and those with chronic, and with ulcerative bronchitis associated with actinomyces were all given a course of intratracheal penicillin<sup>2</sup> (usually 30,000 to 50,000 units of sodium penicillin in a saline suspension daily for a period of three weeks) with marked benefit. In most of these patients the chronic productive cough cleared markedly and in several the actinomyces could no longer be isolated from bronchoscopic specimens.

The patients with chronic bronchopulmonary infections, apart from those having bronchiectasis, chronic bronchitis, and suppuration distal to obstructing carcinomas will be discussed with greater detail. Only those 20 patients from whom actinomyces were isolated bronchoscopically from bronchial exudates or from chest wall sinuses will be considered. Actinomyces in addition to other organisms were isolated in approximately 50 per cent of all patients having chronic lung abscesses and pulmonary suppuration.

The onset of the pulmonary infection was frequently insidious and characterized by a low-grade fever at first that later became septic, a productive cough, pain in the chest, and increasing debility. Bloody sputum was present in all patients at one time or another. The clinical course was characterized by remissions and exacerbations. The onset usually followed episodes of exposure, fatigue, and weight loss associated with combat or military life. In two the pulmonary complaints followed extraction of teeth, and in three upper respiratory infections. Poor oral hygiene had been present in many and was still poor at the time of admission to this hospital. The disease had usually been present for three to six months and in several for over a year prior to the patients' admission. For the most part they had been treated with varying dosages of penicillin and sulfonamides.

Physical examination revealed undernourished, debilitated patients with a foul productive cough. The oral hygiene was invariably poor. Actinomyces were isolated in most instances from tonsillar crypts, from about dirty gums, and in several cases from periapical abscesses. Chest wall sinuses were present in two patients. The pulmonary involvement was unilateral in 15 and bilateral in five patients. Percussion of the lung fields showed dullness to flatness over the involved sites. The breath sounds were usually



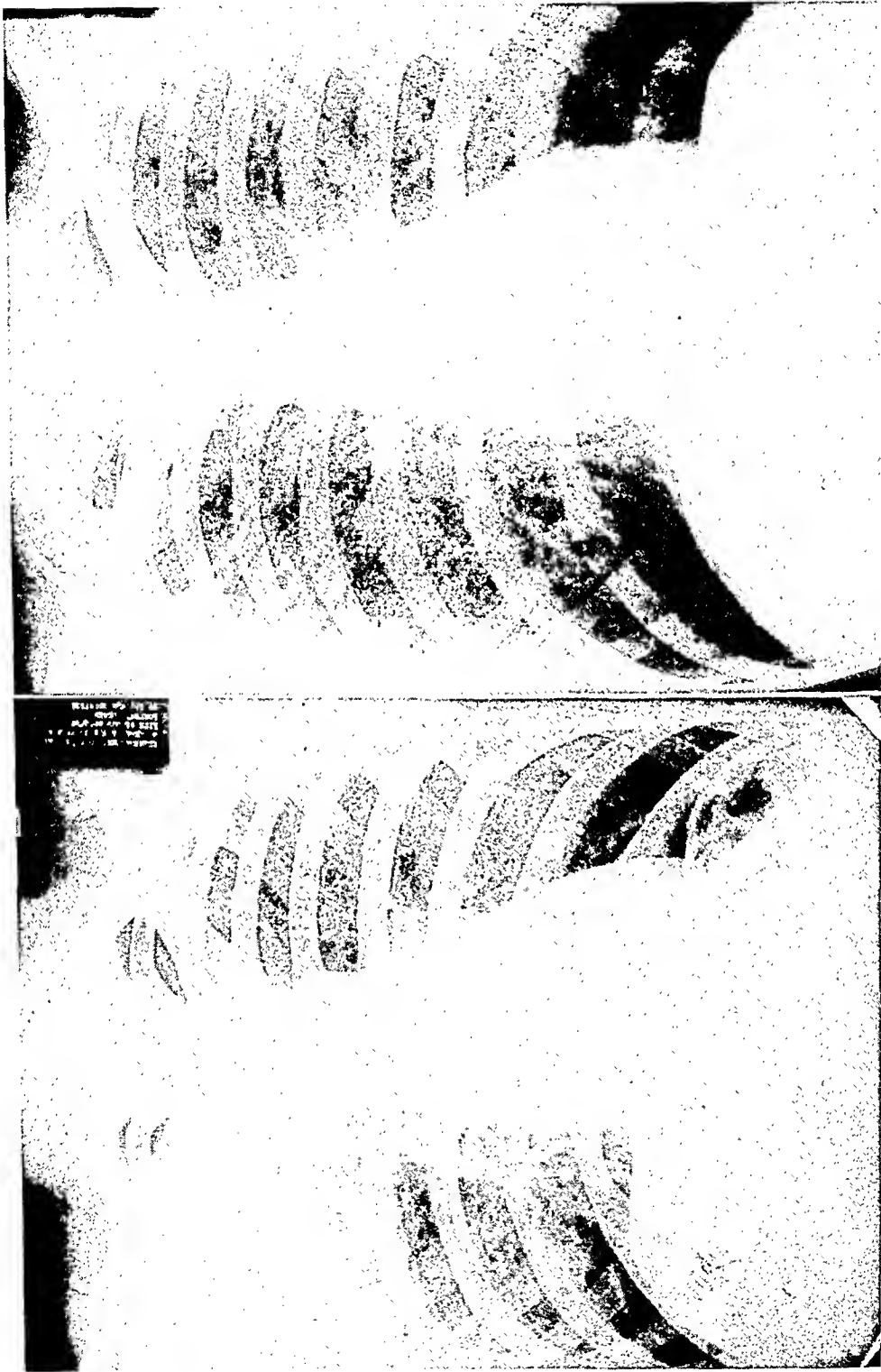
A B  
Fig. 1. Pneumonitis (A) which cleared following a six-week course of intramuscular penicillin therapy. Actinomyces was the predominant organism in both the sputum and bronchial exudate

decreased or bronchial in character. Occasionally amphoric breath sounds were present over areas of cavitation. Moist râles could always be heard. The mid lung field appeared most commonly involved and particularly on the right side. The mid lung field was involved in 10 instances, the upper in seven and the lower in three.

The bronchoscopic appearance of the tracheobronchial tree in these infections was not specific. In some instances the bronchial mucous membrane appeared more hyperemic, granular, and inflamed than usually noted. As much exudate as possible was collected in a bronchoscopic container at the time of bronchoscopy and immediately sent to the laboratory for bacteriological examinations. It was a routine request that all bronchial exudates be carefully studied for fungi and sufficient exudate was supplied to allow adequate examinations. The sputum in these patients varied between one to three ounces daily, was usually yellowish and frequently blood-tinged. Sulfur granules could be seen on direct examination in approximately one-fourth of the specimens. Microscopic identification from the smear was possible in 13 of the 20 cases and in all cases the actinomyces grew on culture. It was of interest to note that gastric washes from two patients were also positive for actinomyces. The presence of actinomyces was usually verified on at least four or five repeated examinations.

The clinical course and response to treatment of patients with chronic pneumonitis, lung abscesses and pulmonary suppuration appeared to depend largely on the chronicity and severity of the infection. All patients were again placed on large doses of penicillin, a combination of penicillin and sulfadiazine, or sulfadiazine alone in an attempt to determine the efficacy of these medications. Though the infection appeared to respond to each of these three methods, penicillin, or penicillin in combination with sulfadiazine appeared most effective. It is essential in such cases that penicillin and sulfadiazine be given in large doses and continued for a long time in spite of roentgen clearing and clinical improvement, otherwise recurrence will take place. Such infections are very resistant to therapy and tend to recur. The dosage of penicillin employed consisted of 50,000 units of penicillin intramuscularly every three hours for 8 to 12 weeks and in some cases even longer. A blood level of 10 milligrams per cent of sulfadiazine was maintained. Preliminary evidence from in vitro experiments suggests that streptomycin is more effective than either penicillin or sulfonamides in inhibiting the growth of actinomyces, but sufficient evidence has not been accumulated for a report at this time.

Those patients (five) with roentgen evidence of pneumonitis without evidence of cavitation who appeared to have good bronchial drainage (figure 1) responded excellently to penicillin and sulfadiazine therapy. All of these patients had had their disease for from three to five months. Large doses of penicillin either alone or in combination with sulfadiazine were again administered for a period of 8 to 12 weeks. Three of these have healed completely and have remained healed for over three to four months. A



B

A

Fig. 2.



C

FIG. 2. Pneumonitis (A) which showed marked clearing following a two-month course of penicillin and sulfadiazine therapy (B), but which recurred soon after this therapy was discontinued (C).

fourth has considerable residual pleural scarring. The fifth patient healed almost completely, but the infection recurred after the penicillin was discontinued. Since this time there has been practically no response to chemotherapeutic measures and surgical treatment will probably be necessary (figure 2).

If cavitation were present (figure 3), less benefit from chemotherapeutic and antibiotic therapy resulted. The general symptoms of toxicity were allayed and there was marked symptomatic improvement. This was frequently associated with roentgen clearing of the pneumonitis surrounding the cavitation. In only one patient did the abscess heal on conservative measures alone. Three patients healed following surgical drainage in conjunction with penicillin or sulfadiazine. One patient following drainage continues to have residual pneumonitis and a draining sinus. Two other patients noted partial improvement following drainage but pneumonitis and cavitation persisted and resection of the diseased tissue by lobectomy was



required. In no instance was the postoperative course complicated by actinomycotic involvement.

In more extensive cases of pulmonary suppuration (figure 4), similar response to conservative measures was noted. Pneumonectomy was necessary in two patients before healing occurred and resection of the diseased tissue by lobectomy was performed in two other instances. Both of the latter cases had previously had drainages of lung abscesses with only partial benefit. Four of the six patients having pulmonary resections were treated postoperatively with sulfadiazine in combination with penicillin and the other two with penicillin alone. Two patients have now been well for over a year, the others except one for a period of three to eight months. It is too soon after operation to evaluate one patient but his condition to date (six weeks) is satisfactory. In the remaining patients it is felt that resection of the diseased tissue will also be necessary before healing will take place.

The involved pulmonary tissue at operation appeared to be markedly consolidated and fibrotic. Extensive pleural adhesions and symphyses were present in five of the six patients operated upon. The pulmonary fissures were obliterated by adhesions and inflammatory tissue necessitating in several instances transection between clamps. Examination of the surgical specimen again showed marked fibrosis about multiple necrotic and burrowing abscesses, the walls of which were covered by dirty, grayish-appearing granulation tissue. The actinomyces was readily isolated from these abscesses in each case.

One patient with draining chest wall sinuses secondary to pulmonary and pleural involvement healed after a four-week course of sulfadiazine (figure 5). After approximately five months a lumbar abscess developed which has required multiple drainages. Evidence of infection is still present. A second patient with multiple rib involvement drains intermittently.

#### SUMMARY

*Actinomyces israeli* is commonly found in chronic bronchopulmonary infections. Careful examinations in 240 patients treated over a six-month period revealed that 109 of these patients had this organism present in sputum specimens, 65 of these patients also had this organism isolated from bronchial exudates obtained bronchoscopically. In approximately 50 per cent of the patients treated who had bronchiectasis, aspiration pneumonia, lung abscesses, and pulmonary suppuration, the actinomyces was isolated in addition to other organisms. It is felt that the presence of the ray fungus is less of a factor in influencing the clinical course, response to treatment, and prognosis of chronic bronchopulmonary infections than the mechanical factors of bronchial occlusion, tissue destruction, avascularity, and fibrosis. It is debatable as to whether such cases should be classified as pulmonary actinomycosis or rather as aspiration pneumonia, lung abscesses, or pulmonary suppuration in which this fungus is present.



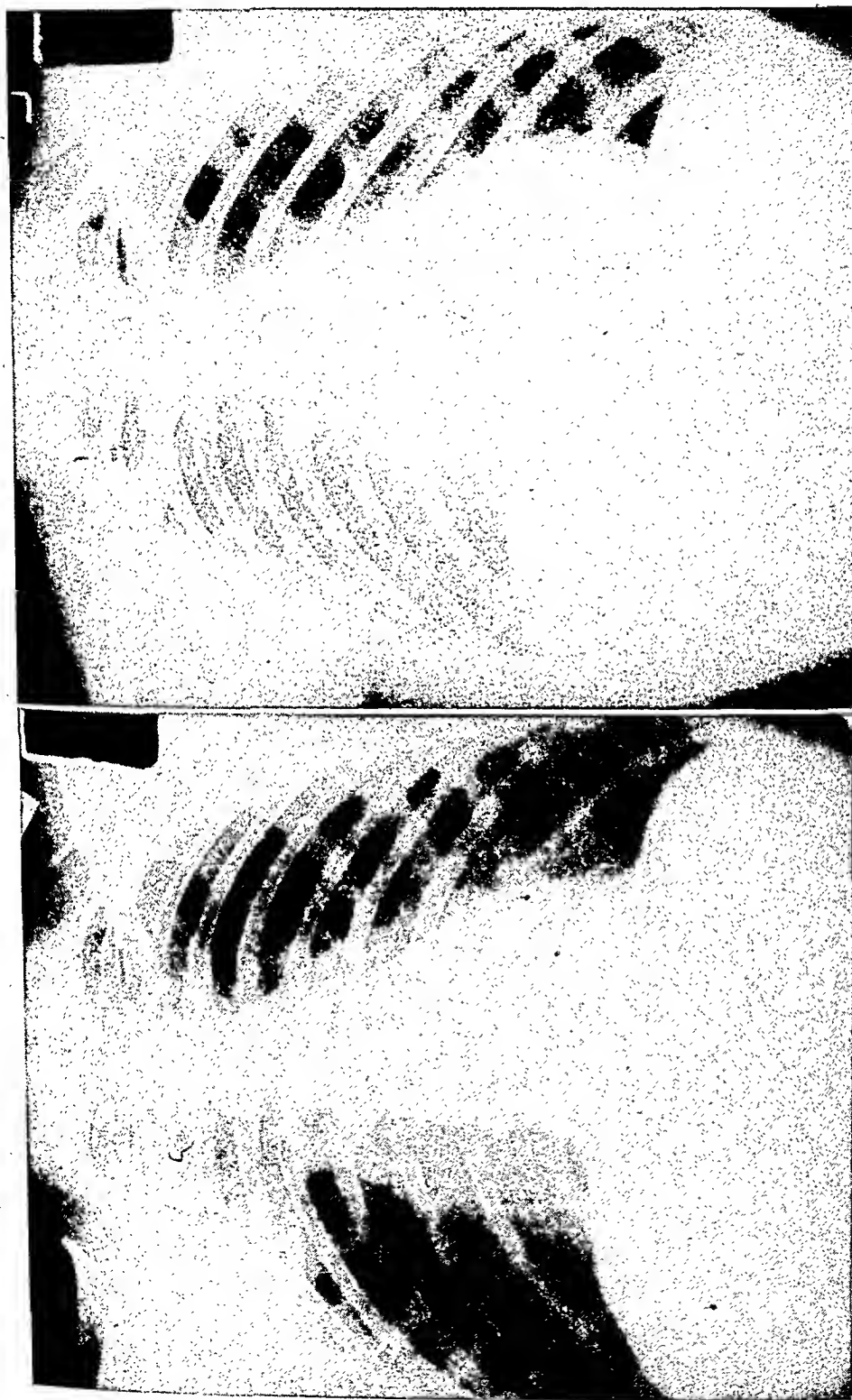
FIG. 3. Lung abscess of six months' duration (A) which had shown no response to chemotherapy or antibiotics. Culture of the abscess at time of drainage showed the actinomycetes to be one of the predominant organisms present. (B) Roentgenogram taken six weeks following drainage.



B

A

FIG. 4.



C

D

FIG. 4. Pulmonary suppuration of eight months' duration (A). The lesion was progressive during repeated courses of penicillin and sulfadiazine therapy (B). Evidence of suppuration persisted following drainage (C). Cure obtained following resection of the upper lobe (D). Actinomyces cultured from the abscesses in the surgical specimen.



B

A

FIG. 5.



C

FIG. 5. Pneumonitis and pleural thickening (A) associated with draining chest wall sinuses (C), which healed following aspiration and a four-week course of sulfadiazine therapy (B).

It was not felt that the presence of the actinomyces influenced significantly the clinical course or that there was any significant difference from other patients in whom the actinomyces were not present. It is realized that *Actinomyces israeli* is an anaerobic organism and under such conditions may predispose to chronicity, and in turn may be partially responsible for the development of chronicity in such infections, but this is also true in varying degrees of other organisms also isolated. All patients were treated similarly without particular reference to this fungus. Operations were performed when indicated and in no patient was actinomyces responsible for any post-operative complication. Apparent cures have now resulted following pneumonectomy in two patients and lobectomy in four patients. Three other patients having abscesses were cured by surgical drainage alone. A discussion of the clinical course and response to both conservative and operative therapy in these patients is presented.

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# CASE REPORTS

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## BANTI'S SYNDROME WITH MULTIPLE ANEURYSMS AND THROMBOSES OF THE SPLENIC BLOOD VESSELS \*

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CONFUSION still exists concerning the pathogenesis and pathologic picture of the disease complex called Banti's syndrome. Two opposing views are held concerning its development. Banti<sup>2</sup> and his adherents considered the splenomegaly to be the primary cause, with liver and vascular changes occurring secondarily. The opposing concept, recently given favor, holds the splenic changes to be secondary to some other cause, usually chronic passive congestion within the portal system. An obstruction is usually described either in the liver, the intra-hepatic blood vessels,<sup>1</sup> the portal circulation or the splenic vein itself.

Banti,<sup>2</sup> in his original descriptions, pointed out that endophlebitis of the splenic, portal and hepatic veins was a part of the pathologic picture but secondary to the splenic disease. Warthin<sup>3</sup> supported the opposing concept in his presentation of cases showing portal vein obstruction as the dominant feature. However, he was unable to reproduce splenomegaly experimentally by ligation of the splenic vein in animals. McMichael<sup>4</sup> introduced "portal hypertension" to explain the pathologic changes seen in the portal vein by comparing their similarity to those seen in arterial hypertension. The recent work of Rousselot<sup>5</sup> Thompson,<sup>6</sup> and Larrabee<sup>7</sup> has advanced "congestive splenomegaly" as the basic condition resulting from hypertension in the portal vein. The obstructive factor causing congestion may be intra-hepatic in the form of cirrhosis, or extra-hepatic in the form of thrombosis, stenosis, external pressure on the vein, congenital malformation or cavernous transformation of the vessel. Of the 65 cases studied by Rousselot 60 per cent showed one of the above causes. In the remaining group an undetermined obstructive factor was postulated.

In addition to sclerosis of the splenic vein, enlargement, tortuosity and varicosities have been repeatedly described. However, less attention has been paid to similar changes which may occur in the splenic artery, as aneurysms, despite the fact that some 100 such cases have been reported by various authors, usually as an incidental finding at autopsy and independent of splenomegaly. Aneurysm of the splenic artery is relatively uncommon, occurring, according to various reports, once in 1500 cases. It may be either single or multiple, saccular or cirroid. Several cases have been cited in which splenomegaly associated with Banti's syndrome has been attributed to the aneurysm. Lossen<sup>9</sup> in 1904 reported such a case in a 24 year old female who had splenomegaly with a cirroid aneurysm of the splenic artery. The splenic vein also showed varicosities. Liver changes were minimal. Baumgartner and Thomas<sup>8</sup> reported a similar case in which

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they considered that the aneurysm, by causing pressure on the splenic vein, resulted in splenic congestion. A similar case was reported by Rudnev.<sup>10</sup> Sanford and Dolly<sup>11</sup> in 1905 described a case in which tortuosity and thrombosis of the splenic vein and a dilated and tortuous splenic artery were considered to be the cause of the splenomegaly. In 1942 Trimble and Hill<sup>12</sup> reported a case in which stenosis of the portal vein and multiple aneurysms of the splenic artery were found. There was no cirrhosis. A review of the literature indicates that enlargement of the splenic artery or vein is not uncommon with splenomegaly. Thus, in the cases of aneurysm of the splenic artery reviewed by Baumgartner and Thomas<sup>8</sup> and Remizov,<sup>13</sup> about half of the cases showed splenomegaly. In a case described by LeFevre and Pettis<sup>14</sup> splenomegaly was diagnosed about three years prior to rupture of the aneurysm. Guy in 1938 reported two similar cases. Whereas some authors believe that the splenic artery aneurysms antecede the splenomegaly, it must also be considered that the arterial changes may be secondary to the splenomegaly.

Few cases of Banti's disease have been reported in recent years in which profound vascular changes were found both in the splenic artery and vein. We are reporting such a case because of its pathologic interest and the possibilities of its interpretation in view of the more recent concepts of the disease.

#### CASE REPORT

A 30 year old white male of Mediterranean extraction was admitted to the U. S. Marine Hospital, Chicago, on July 10, 1944, complaining of an enlarged spleen. He stated he had been in good health until March 10, 1944, when he suddenly became ill with abdominal pain, nausea and vomiting, requiring morphine for relief. He was hospitalized in Belfast, Ireland, and later transferred to a hospital in Scotland where examination revealed an enlarged spleen, the cause of which apparently was not determined. At the time of admission to this hospital he had no complaints except for discomfort due to the enlarged spleen.

The patient's past history is of interest in that he was born in Armenia during the first World War (1915). His family was frequently near starvation and their diet remained deficient until they came to this country in 1922. He had one brother who died of tuberculosis two years after coming to this country.

Physical examination revealed a well developed and well nourished white male who did not appear acutely ill. The spleen extended down to a level just above the umbilicus, was smooth, non-tender. The liver was barely palpable on deep inspiration below the right costal margin.

Laboratory studies showed 4,990,000 red blood cells per cu. mm., 15 grams hemoglobin per 100 c.c. blood, 6,800 white blood cells per cu. mm., with a differential of 26 per cent lymphocytes, 5 per cent monocytes, 57 per cent neutrophils, and 12 per cent stab cells. Blood Wassermann and Kahn tests were negative. Urine was negative. Sedimentation rate was normal. Platelet count was 124,000 per cu. mm. Thick and thin smears for malaria were negative on numerous occasions. Blood culture for *Leishmania donovani* was negative. Tuberculin test was reported positive. Agglutinations for brucellosis were negative in all dilutions. The euglobulin precipitation test for kala-azar was slightly positive but the aldehyde and antimony tests were negative. Total protein was 7.01 grams per 100 c.c. of serum; albumin 5.03, globulin 1.98 grams per 100 c.c. A roentgenogram of the abdomen showed "a very large spleen, the lower border of which reached almost to the iliac crest."



Operation on August 3 revealed an enlarged spleen and a small, atrophic, fibrotic liver with multiple nodules typical of cirrhosis and consistent with Banti's syndrome. The immediate post-operative condition was satisfactory but on the second post-operative day there was a rise in temperature to 105° F. and the patient became irrational, developed evidence of peritonitis, and died on the sixteenth post-operative day.

#### AUTOPSY FINDINGS

The body was that of a youthful male of Mediterranean extraction. The abdomen was distended due to a diffuse peritonitis. The spleen had been previously removed surgically. The liver was small, weighing 1140 grams, with a hobnail surface, and on section it was found to be firm, irregularly fibrosed and greenish-orange-yellow in color. The kidneys showed cloudy swelling. The gastrointestinal tract was intact. No varicosities were found in the esophagus. The superficial blood vessels of the stomach were not engorged. The portal vein was of the usual caliber and

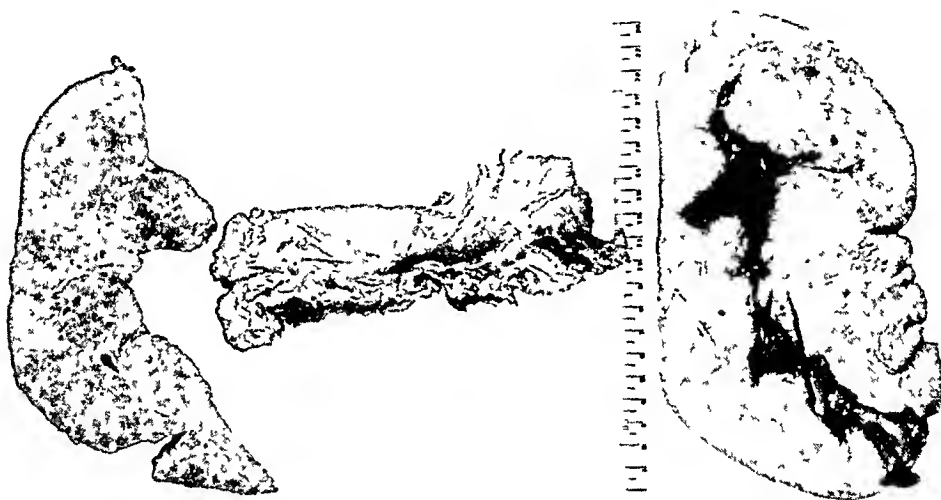


FIG. 1. The cirrhotic liver, varicose splenic vein, tortuosity of splenic artery and splenomegaly.

thin walled. The splenic vein was considerably altered (figures 1 and 2). Near the tail of the pancreas, just before the vessel entered the spleen, it was stenosed over an area of 1.5 cm. so that the circumference was reduced to 4 mm., completely obliterating the lumen. This narrowing was due to dense thickening and fibrosis of the wall. Immediately proximal to this occlusion, overlying the body of the pancreas, there was a varicose dilatation of the vessel producing a sac measuring 4.5 by 6.5 cm. Two smaller sacs filled with recent thrombi, one measuring 3 cm. and the other 2 cm., projected from the larger one. The remaining portion of the splenic vein was dilated (25 mm. in circumference), and thin walled. The splenic artery was tortuous, thickened, and formed multiple, cirroid, telescoping aneurysms. Several smaller saccular aneurysms containing antemortem thrombi projected from the main artery. The wall averaged 25 mm. in circumference, showed atheromatous deposits upon the intima and was thickened. The spleen, which had been previously removed, was considerably enlarged weighing 750 grams and measuring 20 by 11 cm. after fixation in formaldehyde. The capsule was thickened and on section the surface was found to be bloody but the consistency of the organ was firm.

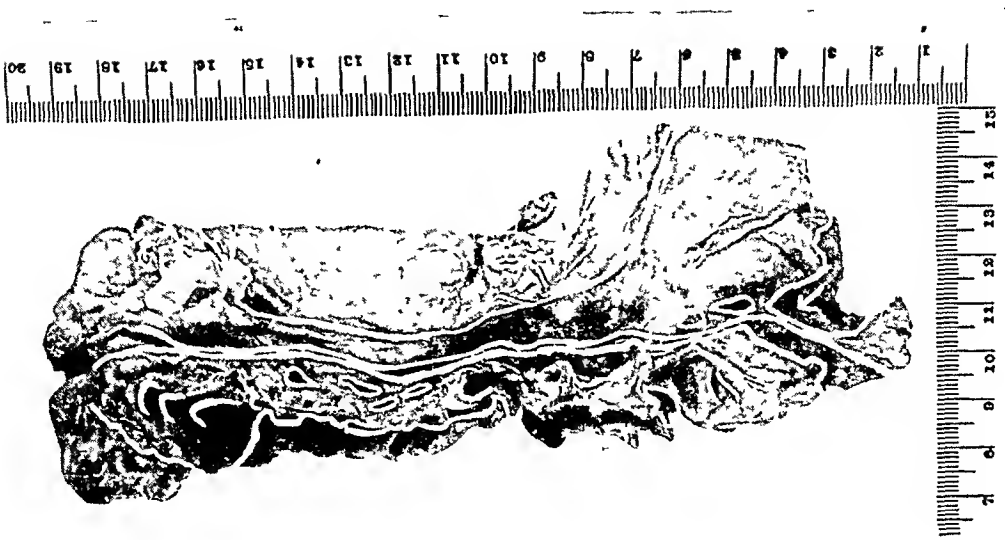


FIG. 2. Splenic blood vessels viewed from posterior. Upper vessel is splenic vein and portal vein. Arrow points to the stenosis and immediately distal to it is the varix and smaller sacs. Lower vessel is the dilated, tortuous artery with multiple small aneurysms.

Microscopically the liver showed the findings encountered in a Laennec type of cirrhosis and the spleen showed "fibroadenie" and the other changes described by Banti. The wall of the splenic vein was fibrosed and hyalinized. At the site of the stenosis, in addition to these alterations, calcification was also present. The splenic artery showed considerable thickening of the muscularis with increase of connective tissue.

### DISCUSSION

One cannot, from the pathologic findings, draw any conclusions concerning the course of disease in this case. However, it is interesting to consider the possibilities involved. According to Banti's concept the splenomegaly would be the initiating factor. An unknown toxin would damage the splenic vessels and finally involve the liver. Proof of a toxin capable of doing this is lacking in this case as in others reported. Stenosis of the splenic vein, according to Rousselot and others, could initiate a congestive splenomegaly in which case the liver cirrhosis would be entirely coincidental. The aneurysms of the splenic artery might be considered as spontaneous and a cause of pressure upon the splenic vein. However, there is no indication that the aneurysms encroached upon the vein or anteceded the other described changes. Cases cited in the literature in which aneurysms of the splenic artery have been considered capable of such pressure on the splenic vein are not convincing. Because the stenosis of the splenic vein anatomically was found to be of long standing, Warthin's<sup>3</sup> concept might be applied in this case. Accordingly, the obstructive changes of the splenic vein would be primary, the splenomegaly would be the result of congestion. The interpretation of this case which best explains all the findings would attach primary importance to the cirrhosis. Recent work points to nutritional deficiencies as important etiological factors in cirrhosis. Of particular significance in this case is the fact that the patient was Armenian and in his

childhood subjected to the extreme starvation which was inflicted on these unfortunate people in World War I. Whether this starvation was sufficient and of long enough standing to instigate a cirrhosis is problematical. Nevertheless, assuming that the cirrhosis was the primary factor, a splenomegaly of some degree could be expected from the portal congestion. This same congestion might also cause sufficient sclerotic changes in the vessel wall to produce ultimately a stenosis. The additional obstruction thus produced might then account for the advanced splenomegaly seen in this case. The varicosities of the splenic vein might result from hypertension proximal to the obstruction. Fibrosis of the spleen and splenic vein could then demand a sufficient increase in blood flow from the arterial side to result in atheromatous changes such as are found in any arterial hypertension. Aneurysmal formations could be the sequelae of these alterations.

Thus, we have a case of Banti's disease which presents a complete complex of findings which are in the form of a circle rather than a chain of events. One may point to any one of the pathologic findings and incriminate it as the initial cause. It has been presented because of its widespread ramifications rather than in an attempt to prove any one factor as responsible for Banti's syndrome.

#### SUMMARY

A case of Banti's syndrome has been presented which demonstrates cirrhosis of the liver, splenomegaly, thrombosis, varicosities and dilatation of the splenic vein, and multiple aneurysms and tortuosity of the splenic artery. The various possible explanations for this complex have been considered. The case emphasizes the profound changes which may occur in the splenic circulation in this disease.

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## WATERHOUSE-FRIDERICHSEN SYNDROME: RECOVERY FROM SHOCK IN FATAL CASE\*

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### INTRODUCTION

THE dramatic and usually fatal sudden circulatory collapse appearing in cases of fulminating septicemia (usually meningococcic) associated with adrenal hemorrhage has been most commonly recognized under the name Waterhouse-Friderichsen syndrome. The recognition and delineation of this condition has followed the course of most of the diseases which have yielded to clinical elucidation. First only scattered cases were reported and compared. Then as the condition became more widely known, it was more commonly recognized so that of the approximately 175 cases now in literature, over half were reported in the last five years.<sup>1</sup> Most of these have been in children although at least 40 cases in adults have also been recorded.<sup>1</sup> Increasingly, now, attempts are being made to classify cases according to various clinical and pathological criteria and to trace the pathogenesis of the disease. This, in turn, is leading to a rational approach to therapy.

The somewhat diversified concepts of the pathogenesis of this condition which have been presented in recent reports may be briefly synthesized as follows. A primary bacteremia develops with the usual manifestations of an acute febrile illness. The bacterial infection overwhelms the primary hematogenous defenses and in some cases bacterial growth is so rapid that phagocytized meningococci may be seen within leukocytes in direct smears of the peripheral blood.<sup>2</sup> Various manifestations of severe damage to the vascular system then appear; the most important of these are medical shock and hemorrhages of the adrenals, skin and other sites. Since hemoconcentration apparently does not occur and blood loss is relatively insignificant, the profound medical shock is probably due to generalized vasodilatation. This is manifested peripherally by striking variegated cyanosis. It is in the shock phase that most cases succumb. Heroic therapeutic measures are necessary to compensate for the disparity between the circulating blood volume and the dilated peripheral vascular bed.

In several reports<sup>3-6</sup> the importance of shock has been emphasized and the

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adrenal damage has been considered to be secondary and coincidental. It has been shown by Williams<sup>7</sup> and emphasized by others<sup>8</sup> that death may supervene in meningococcemia with the classical clinical picture of shock and purpura but without adrenal hemorrhages. According to this concept, even a case with adrenal hemorrhages should be considered primarily as a bacteremia and its designation as a case of Waterhouse-Friderichsen syndrome on the basis of minor adrenal hemorrhages becomes a matter of etymological quibbling. On the other hand, there are cases in which extensive adrenal damage has occurred and it is important to attempt to determine its clinical effect. The vasopressor function of the adrenal cortex is now widely recognized. Rich<sup>9</sup> has pointed out that in experimental animals and in cases of Addison's disease, adrenal cortical deficiency is aggravated very rapidly by acute infections. Weil and Brown<sup>10</sup> have demonstrated an increased urinary excretion of cortin-like elements during acute infections.

Adrenal damage due to causes other than hemorrhage has been reported in acute infections with the clinical picture of Waterhouse-Friderichsen syndrome. Rich<sup>9</sup> reported cortical cellular necrosis with the conversion of the solid cords of cells into tubular structures. Banks and McCartney<sup>11</sup> described cases of thrombotic necrosis of the adrenals and of focal adrenalitis.

All of these pathologic changes in the adrenals must contribute to the severity of the medical shock which, in most cases, is directly responsible for death. The chances for recovery from shock are decreased by adrenal damage. This distinction is important in evaluating the cases of recovery from the Waterhouse-Friderichsen syndrome which have been reported recently.<sup>12-16</sup> In very few of these cases was clinical evidence of adrenal damage demonstrated following recovery from the acute phase of the illness. That recovery from the shock phase of this disease even in the presence of adrenal damage can occur has also been demonstrated by Marangoni and D'Agati<sup>17,18</sup> who had two cases who recovered from shock only to die subsequently with severe toxic damage to the liver and kidneys in addition to adrenal hemorrhages.

The purpose of this paper is to report a case similar to those of Marangoni and D'Agati.

#### CASE REPORT

The patient was a 43 year old white riverboat engineer whose final admission to the hospital was on January 9, 1945, at 9:05 a.m.

Family history was noncontributory.

He had had five previous admissions since 1937 with the following diagnoses: lung abscess of right lower lobe, common cold, pneumonia, pleurisy of left side, and otitis media. The recovery from each of these conditions was considered good. In 1944 he had three attacks of acute febrile illnesses thought to be pneumonia for which he was hospitalized elsewhere with a prompt recovery. Twenty-four hours before his final admission he developed chills, fever, abdominal pain, vomiting, and severe headache. These symptoms progressed rapidly until he became irrational and then semicomatose during the night before admission.

Physical examination showed a semicomatose, apathetic white male with ashen-gray facies lying quietly in bed responding resentfully and in monosyllables to questioning. Temperature was 35.5° C. Blood pressure was 70 mm. Hg systolic and 50 mm. diastolic. The pulse was 84 per minute and the heart sounds were faint. The mucosa and skin showed evidences of marked dehydration. Scattered over the

entire body surface were many small petechiae ranging from the size of a pinhead to one-half inch in diameter. A few crepitant râles were heard in the axillae but otherwise the lungs were normal. Slight right epigastric tenderness was present. Minimal pitting edema of the legs was noted. Neurological examination on admission was negative except for questionably positive Kernig and Brudzinski signs and within a few hours both of these tests became markedly positive.

Laboratory studies on admission were reported as follows: leukocytes 44,500 per cu. cm. with 90 per cent neutrophils and 10 per cent lymphocytes; erythrocytes 4,530,000 per cu. cm.; hemoglobin 77 per cent; blood sugar 232 mg. per cent; non-protein nitrogen 43 mg. per cent; creatinine 2.6 mg. per cent; malaria smear negative; smear of blood from petechia on right ankle contained gram-negative diplococci within leukocytes; spinal fluid contained 44,000 leukocytes per cu. cm. and smears showed intracellular gram-negative diplococci; blood culture was positive for meningococci.

A spinal puncture was performed soon after admission. The spinal fluid was cloudy with a pressure of 310 mm. of H<sub>2</sub>O and a normal Queckenstedt response. One hundred thousand units of penicillin were introduced intrathecally. The patient was also given 5 gm. of sodium sulfathiazole and another 100,000 units of penicillin intravenously. He then received 15,000 units of penicillin every three hours intramuscularly and 1 gm. of sulfadiazine every four hours. Eschatin 1 c.c. was given intramuscularly every four hours and an almost constant flow of intravenous fluids was maintained.

Eight hours after admission the patient was definitely out of shock; he was quiet but still somewhat incoherent. The temperature had risen to 38° C. (axillary). The pulse was 88 per minute, respirations 26 per minute, and the blood pressure 135 mm. Hg systolic and 60 mm. diastolic. Fourteen hours after admission his temperature had risen to 40.5° C. (axillary), the pulse was 120 per minute, and the respirations 40 per minute with a definite Cheyne Stokes pattern. He was profoundly comatose. About this time he developed gross and microscopic hematuria and was incontinent. In spite of continued therapy his condition became steadily worse and he died 24 hours after his admission and 48 hours after the onset of his illness.

Postmortem examination was performed seven hours after death; permission to examine the head was not obtained. Gross examination revealed the following positive findings. Petechiae ranging from 1 mm. to 8 mm. were found in the conjunctivae and skin especially around the ankles. The lungs were extremely congested and edematous having a uniform dark red color with thin sero-sanguineous fluid oozing from the cut surfaces. Several bronchiectatic dilatations were noticed in the right lower lobe. The heart appeared dilated with a soft, flabby, dull brown myocardium. Scattered over the epicardium were many petechiae. The parenchyma of the liver, spleen, and kidney was soft and apparently congested. Scattered through the renal parenchyma were reddish spots resembling hemorrhages. The left adrenal was somewhat enlarged but the right was approximately normal in size. The cortico-medullary boundaries were sharply defined. Scattered through the cortices and especially at the cortico-medullary boundaries were numerous areas of hemorrhagic degeneration measuring 1 to 3 mm. in diameter.

Microscopic examination showed the following significant positive findings.

*Lung:* The alveolar walls were moderately thickened with dilatation and congestion of the capillaries and extensive extravasation of blood and edema fluid into the interstitial tissues and into some alveoli. Other alveoli were air containing. The pleura was moderately thickened and its capillaries were congested.

*Heart:* The myocardium contained occasional small focal aggregations of neutrophils and some muscle bundles had a fibrillar appearance with loss of staining quality. Neutrophils were also scattered along the endocardium and at one place neutrophils

and fibroblasts had collected to form a small mass projecting into the ventricle. All blood vessels were dilated and one showed intimal proliferation.

*Liver:* Most of the blood vessels and especially the central veins were distended with blood. Moderate fat was seen in the central zones of the lobules and a slight increase in the lymphocytes in the spaces was noted.

*Spleen:* The architecture was normal except for the presence of erythrocytic congestion and a scattering of neutrophils in the red pulp.

*Kidney:* The glomeruli appeared generally swollen. This was noted both in the capillary tufts and the epithelial linings, but the tuft capillaries were not unusually congested. At several points Bowman's capsules contained finely fibrillar, noncellular exudate. Occasional tubules contained blood and the tubular epithelium as a whole showed degenerative changes. The vessels generally were blood-filled and the larger arteries showed slight, irregular endothelial proliferation.

*Adrenals:* The sinusoids and capillaries were extremely congested. Many hemorrhagic areas were scattered throughout the cortex, especially in the zona fasciculata and zona reticulata. In these areas of hemorrhage there was disruption of the cellular architecture. Most of the cortical cells showed vacuolation and irregular staining of their cytoplasm and pyknosis or pale hyalinization of their nuclei. In the zona glomerulosa there were several discrete foci of polymorphonuclear infiltration in areas of partial or complete cellular destruction lying between the sinusoids. A careful search of specially stained slides failed to reveal any bacteria.

## DISCUSSION

This case is presented as another example of recovery from shock in a case of Waterhouse-Friderichsen syndrome with an eventually fatal termination. It again demonstrates that with vigorous therapy these patients may recover from the shock phase of the syndrome, thus supporting the claims of those authors whose cases have gone on to final and complete recovery. It further shows that there is a second critical period in the recovery from this condition which is caused by damage to other organs especially the liver and kidneys (as shown by Marangoni and D'Agati<sup>17, 18</sup>) and also the lung, heart, and other viscera. Perhaps an important factor is the damage to the brain as pointed out by Banks and McCartney<sup>11</sup> in their "encephalitic" group of cases. Unfortunately we were unable to demonstrate this. This damage occurs not only because of the acute "toxic" action of the infectious agent, but also because of tissue anoxemia occurring as a result of impaired circulation during the shock phase of the disease.

As to the pathogenesis of the adrenal damage we would like to point out in this case the presence of "focal adrenalitis" in addition to hemorrhages. The localization of these areas suggests that hemorrhage may be secondary to damage to the adrenal cortical cells which form the walls of the sinusoids.

## SUMMARY

A case of Waterhouse-Friderichsen syndrome in an adult has been presented. This patient lived for almost 48 hours after the onset of his illness; he recovered from the primary shock phase of his illness only to die in the febrile and toxic secondary phase.

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### FATALITY IN A BLOOD DONOR; A CASE REPORT, WITH A REVIEW OF THE LITERATURE\*

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THE American Red Cross through its Blood Donor Centers collected approximately 13 million pints of blood during the period between 1941 and 1945. At the Chicago Blood Donor Center approximately 640,000 pints of blood were collected in the three and a half years of its operation.

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From the American Red Cross Blood Donor Center, Chicago, Ill.



On each donor a history was taken and a brief physical examination was made so as not to accept a donor with an acute infection or serious chronic illness. Many donors, however, withheld or denied information relative to their physical condition, so that they would not be rejected.

There has occurred only one fatality in a blood donor at any of the American Red Cross blood donor centers or any mobile unit station during this entire project. This fatality is presented.

#### CASE REPORT

A white male, age 43, weight 55 kg., height 160 cm., presented himself for his fifth blood donation. All the donor requirements were fulfilled. There were no technical difficulties encountered during the venesection, and 500 c.c. of blood were readily obtained by the gravity method. No pumping or suction of any kind was used during the entire venesection. A few minutes after the completion of the venesection the donor had a small watery emesis and presented the usual systemic reaction that was observed in about 6 per cent of the donors.<sup>1</sup> The donor was examined by a physician who ordered him moved to the Recovery Room where atropine sulfate gr. 1/150 was administered hypodermically. At this time the blood pressure was 90 mm. of Hg systolic and 60 mm. diastolic; the pulse rate 78, and of moderately good quality. The blood pressure prior to bleeding was 120 systolic and 80 diastolic. A short time later the donor was allowed to sit up on the edge of the bed since he stated that he felt "better." After sitting up several minutes he stated that he now felt "weak," and again was ordered to recline. The blood pressure recorded at this time was 90 systolic and 60 diastolic and the pulse rate was 70. The donor seemed to improve with the change of position when he suddenly complained of slight substernal pressure without radiation, gasped several times and suddenly died. An ampoule of coramine followed by caffeine sodium benzoate (7½ grains) was administered subcutaneously immediately during the "gasping" period.

*Past Medical History.* The donor had made four previous donations of 500 c.c. each without any consequences. The last donation was made eight months previously. The donor's wife later stated that about one month prior to the last donation the donor had experienced substernal pain of short duration but did not seek any medical care at that time. He did not admit the above history of substernal pain at the admission examination prior to the donation. No history of previous fainting or known sensitivity to any drugs was obtained at any time. Clinical impression as to cause of death: Acute myocardial infarction due to acute coronary occlusion.

#### AUTOPSY \*

An autopsy was performed several hours post mortem, and the conditions observed were as follows:

Chest: The pleural cavities were free of fluid. The lungs were moderately distended, purple gray and subcrepitant. On cut surface they were moderately moist with frothy fluid. Heart: The pericardial sac contained a few c.c. of clear fluid. The myocardium was soft and purple gray. The valves were unchanged. The aorta smooth throughout. Coronary arteries: The left circumflex artery was smooth and thin walled. The left descending branch had at a point 2 cm. from its origin a hyaline thickening 1 cm. long with a slight calcification. In the middle of this thickening the lumen was narrowed to pin-point size and would not admit the finest scissors.

\* Dr. Victor Levine, pathologist for the Cook County (Ill.) Coroner, performed the autopsy and furnished the Autopsy Report.

The right coronary had, at a point 3 cm. from its origin, a hyaline and calcified thickening 1.6 cm. long. In the first centimeter of this thickening the lumen was irregularly ulcerated and occluded by a loosely adherent purple gray blood clot 7 mm. long. Just beyond this occlusion, but still within the region of the thickening the lumen was markedly narrowed to pin-point size and would not admit the finest scissors. Beyond the narrowed portions of both coronaries, the lumen widened out to normal and the walls were thin and smooth. On the posterior wall of the right ventricle there was an indistinct zone 5 cm. in width in which the cut surface of the myocardium showed scattered gray, firm areas 1 to 2 mm. in diameter of early fibrosis. The intervening muscle had a slight brown discoloration but no solid single infarcted area could be definitely demarcated.

Abdomen: The liver weighed 1500 gm., and was distended, fairly firm and purple brown. The spleen weighed 150 gm., and was fairly firm and deep purple. The kidneys weighed about 300 gm. together, and were dark purple gray with fairly distinct vascular marking on the cut surfaces. In the other abdominal organs nothing of note was observed.

*Anatomic Diagnosis.* 1. Thrombotic occlusion of right coronary artery. 2. Marked coronary sclerosis with narrowing of both the left descending and the right coronary arteries. 3. Focal fibrosis of posterior wall of right ventricle. 4. Edema of lungs. 5. Acute passive congestion of liver, spleen and kidneys.

### DISCUSSION

Death occurring during or immediately after blood donation is very infrequent, and is seldom reported in the literature when it does occur. A review of the literature was made to ascertain the cause of death in blood donors.

Since a possible contributing factor in coronary occlusion may be the slowing of the systemic circulation, and since the coronary flow is regulated by the mean level of the arterial pressure,<sup>2,3</sup> especially the diastolic pressure, any marked fall in blood pressure may act as a precipitating cause of coronary thrombosis.

Approximately 6 per cent of the blood donors at the Chicago Blood Donor Center developed a systemic reaction<sup>1</sup> varying from slight to marked pallor, weakness, faintness, sweating, nausea and vomiting, with a transient drop in blood pressure. That the above symptoms occur during the drop in blood pressure has been demonstrated by Engel<sup>4</sup> and his coworkers, who further felt that in vasodepressor syncope provoked by venepuncture the primary reaction was a fall in blood pressure.

In the presence of coronary sclerosis there is a tendency to hypersensitivity of the vagal type of carotid sinus reflex.<sup>5</sup> It should be pointed out that the numerous emergency functions and the reserve capacity of the normal cardiovascular system enables a normal person readily to recover from a "faint," but derangements in the circulatory dynamics in an already damaged cardiovascular system which is unable to cope with a sudden drop in blood pressure may lead to the so-called "fatal" syncope.<sup>5</sup>

Masters<sup>6</sup> felt that regardless of whether coronary thrombosis took place on an arteriosclerotic basis or as a result of hemorrhage into a plaque, it could be attributable to alterations in the coronary circulation. These changes could be in blood volume, pressure and speed of flow within the arteries or changes in the physical and chemical properties of the blood. That such changes may occur following "syncope," i.e., transient drop in blood pressure with reduction of the

venous return to the heart <sup>7</sup> and diminished cardiac output which in turn result in decrease in speed and volume of coronary flow, is well established.

Nathanson,<sup>8</sup> in reviewing 142 autopsies showing occlusive coronary disease in which sudden death occurred, stated that death was explained on a "physiological" basis. In his report the preponderance of evidence indicated that cardiac standstill was the basis of temporary cardiac syncope, and ventricular fibrillation was the mechanism underlying the fatal syncope or sudden death of coronary disease.

Englehardt and Sodeman <sup>9</sup> have discussed syncope on exertion and its relationship to coronary artery disease with possible resultant occlusion of the right coronary artery which may interfere with the circulation to the Bundle of His and so cause various degrees of heart-block.

Cookson <sup>10</sup> in 200 proved cases of myocardial infarction pointed out that syncopal symptoms were present in 15 of these cases. In 10 cases the myocardial infarction was ushered in by syncopal symptoms. Vomiting was almost invariably present in the syncopal cases. In his series the prognosis for the cardiac infarction with syncopal onset seemed to be more serious than usual. At the onset of the myocardial infarction associated with syncope the appearance of the patient was that of severe peripheral circulatory failure often combined with a slow heart rate. Substernal pain was slight or absent.

Boyton and Taylor <sup>11</sup> in their report from the Blood Donor Service of The American Red Cross, which was dated as of April, 1944, and represented experience with approximately three and one-half million donors, stated that no death attributable to cardiovascular causes had occurred in any Blood Donor Center or at any Mobile Unit Station. In their report there were 10 deaths which occurred 48 hours after donation. In five cases a history of cardiovascular disease had existed but had been denied by the donor at the preliminary examination. Of the 10 fatal cases, seven were males, and three females. One donor was a seven time donor. The clinical diagnoses were probable coronary thrombosis in eight cases, and cerebral hemorrhage in two. In the single case in which an autopsy was performed the anatomic diagnosis was coronary sclerosis with acute cardiac dilation. In seven of the eight cases in which the clinical diagnosis of coronary thrombosis was made, death had occurred within four to eight hours after donation. Boyton and Taylor felt that these fatalities were actually coincidental and unrelated to the donation and that the normal expectancy for cardiovascular accidents of this nature is far greater than the experience of the Blood Donor Centers, regardless as to whether or not the factor of selection was considered.

Browne <sup>12</sup> reported a death in a male blood donor, age not stated, and it was felt that death was due to the injection of a large quantity of air into the vein at the onset of the venesection. An autopsy performed failed to show conclusively the cause of death.

In an editorial in the British Medical Journal <sup>13</sup> of August 1941 there was mentioned a death in a blood donor resulting from air embolism in which the use of an electric rotary suction pump described by Biddle and Langley became impaired during the venesection allowing air to enter the circulatory system. This case was not fully reported.

Simpson <sup>14</sup> reported that during a 10 year period, 1932 to 1942, there were

56 fatal cases of air embolism examined for medico-legal purposes, and that death during venesection accounted for four of these cases. No further details concerning these four cases were mentioned.

Montgomery<sup>15</sup> discussed the cause of death of a professional blood donor occurring 29 days after donation. The autopsy revealed multiple emboli, i.e. cerebral, mesenteric, and splenic.

Hines and Kessler,<sup>16</sup> in their study of 58 cases in which either the electrocardiographic or postmortem findings were those of coronary thrombosis, found that only 8 per cent of these cases had a red blood count lower than 4.5 million, and only 16 per cent had a hemoglobin less than 13 grams. In their series only two of the 58 cases of coronary thrombosis had an erythrocyte count less than 4 million. They also noted that there was a diminished clotting time and shortened prothrombin time in patients with high erythrocyte counts, and showed that similar changes in clotting mechanism had been observed in patients known to have thrombosis at various sites. Hines and Kessler were able to lower the erythrocyte count and the hemoglobin level by repeated small venesections. On the basis of their experience with a small series of cases they felt that repeated venesections of small amounts was a rational treatment for the prevention and treatment of coronary thrombosis.

### SUMMARY

A review of the literature reveals that the reported causes of death in blood donors were either air embolism or cardiovascular lesions such as coronary thrombosis, cerebral hemorrhage, or other arterial emboli. A case is presented in whom postmortem examination revealed marked coronary sclerosis and narrowing of both the left and the right coronary arteries with myocardial lesions of variable duration prior to the venesection.

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## FATAL SPONTANEOUS HEMOPNEUMOTHORAX: REVIEW OF THE LITERATURE AND REPORT OF A CASE \*

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SPONTANEOUS hemopneumothorax in the absence of active tuberculosis is relatively uncommon. Hartzell <sup>1</sup> in 1942, in an excellent review of the subject, found only 40 cases in the literature and added three of his own. Fatal hemorrhage in spontaneous pneumothorax is even more rare. We have been able to find only 13 such instances on record that were confirmed by necropsy. Moreover, in these patients, postmortem examination not infrequently failed to reveal the origin of the lethal bleeding.

Because of the apparent rarity of fatal cases and since only four of them were studied microscopically, we felt that the report of an additional case might re-emphasize and perhaps assist in clarifying certain obscure features in the pathogenesis of this disease.

### CASE REPORT

A Lieutenant Commander in the Navy, aged 30, had always been well until five days prior to admission to the hospital, when he experienced pain in the left supra-clavicular region after slinging a heavy bag over his left shoulder. Following this he had no particular symptoms until 2 a.m. on the morning of admission to the hospital, when he had a sudden severe pain throughout the left chest accompanied by weakness and difficulty in breathing. He was first seen by a civilian physician at 9:30 a.m., who advised immediate hospitalization. He was admitted to the hospital on a stretcher at 11 a.m. and, on examination, was found to be in profound shock and extreme respiratory distress. There was limited excursion of the left chest and on percussion it was hyperresonant, except for increased dullness at the base. The right chest was normal. The breath sounds were absent over the left chest and the heart and trachea were displaced markedly to the right. Heart sounds were heard to the right of the sternum which were regular but muffled. The pulse was very rapid and almost imperceptible and the blood pressure could not be obtained. He was given morphine and placed in an oxygen tent, and a total of 1000 c.c. of blood plasma was administered over a period of three hours. Roentgenogram of the chest revealed complete collapse of the left lung and fluid in the pleural cavity. Five hundred c.c. of blood were aspirated from the left chest cavity. The patient became comfortable, his respiratory distress

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FIG. 1. Low power photomicrograph of visceral pleura with adhesions. Note prominence of mesothelium and deposits of fibrin and leukocytes about adhesions.  $\times 145$ . (Courtesy of the Army Medical Museum.)

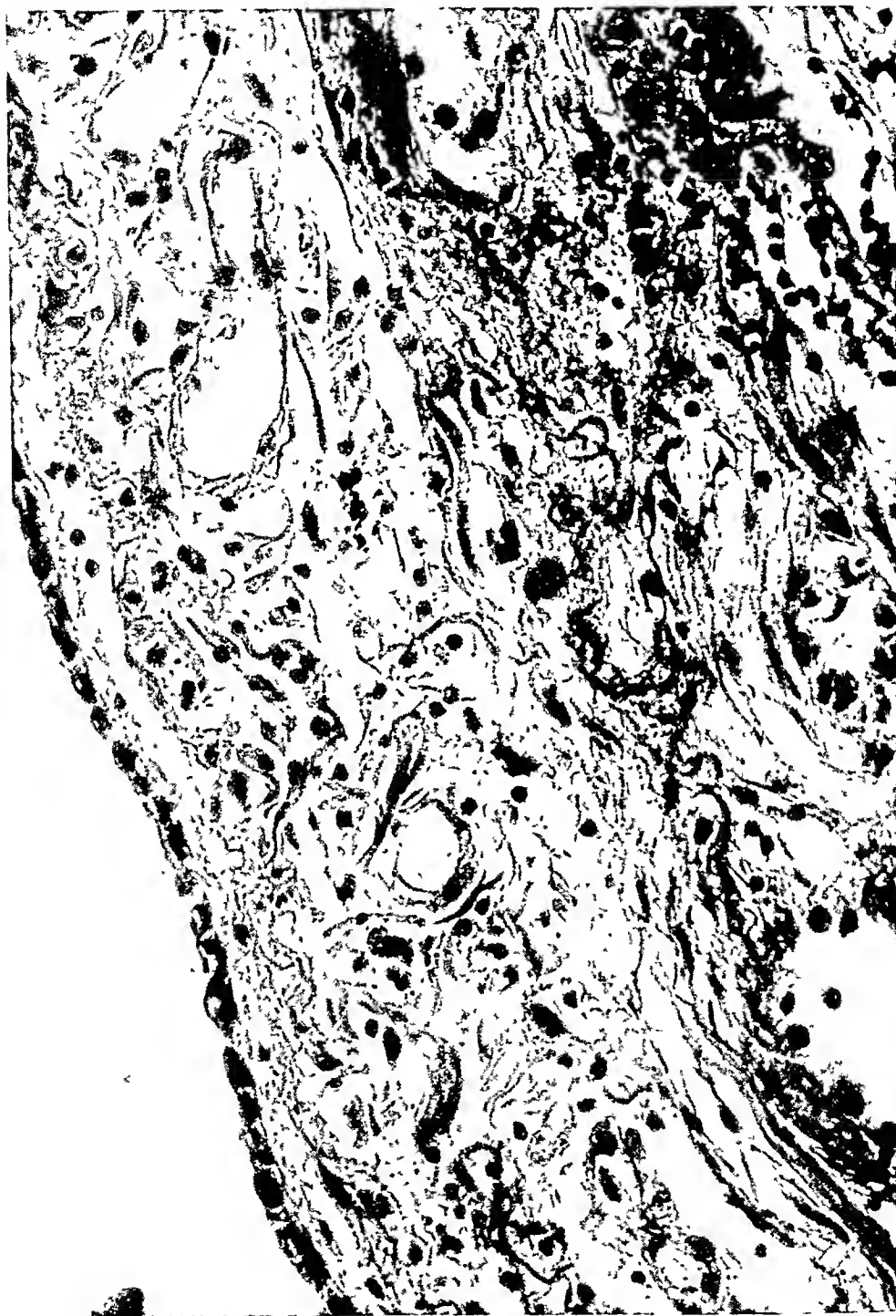


FIG. 2. High power photomicrograph of visceral pleura abutting upon adhesion, showing mesothelial swelling, pleural thickening, increased vascularity, fibrin deposits and leukocytic infiltration.  $\times 500$ . (Courtesy of the Army Medical Museum.)





FIG. 3. Low power photomicrograph of parietal pleura showing mesothelial proliferation and marked cellular infiltration with edema near the base of adhesion, along with free blood, fibrin and leukocytes in the pleural space.  $\times 145$ . (Courtesy of the Army Medical Museum.)



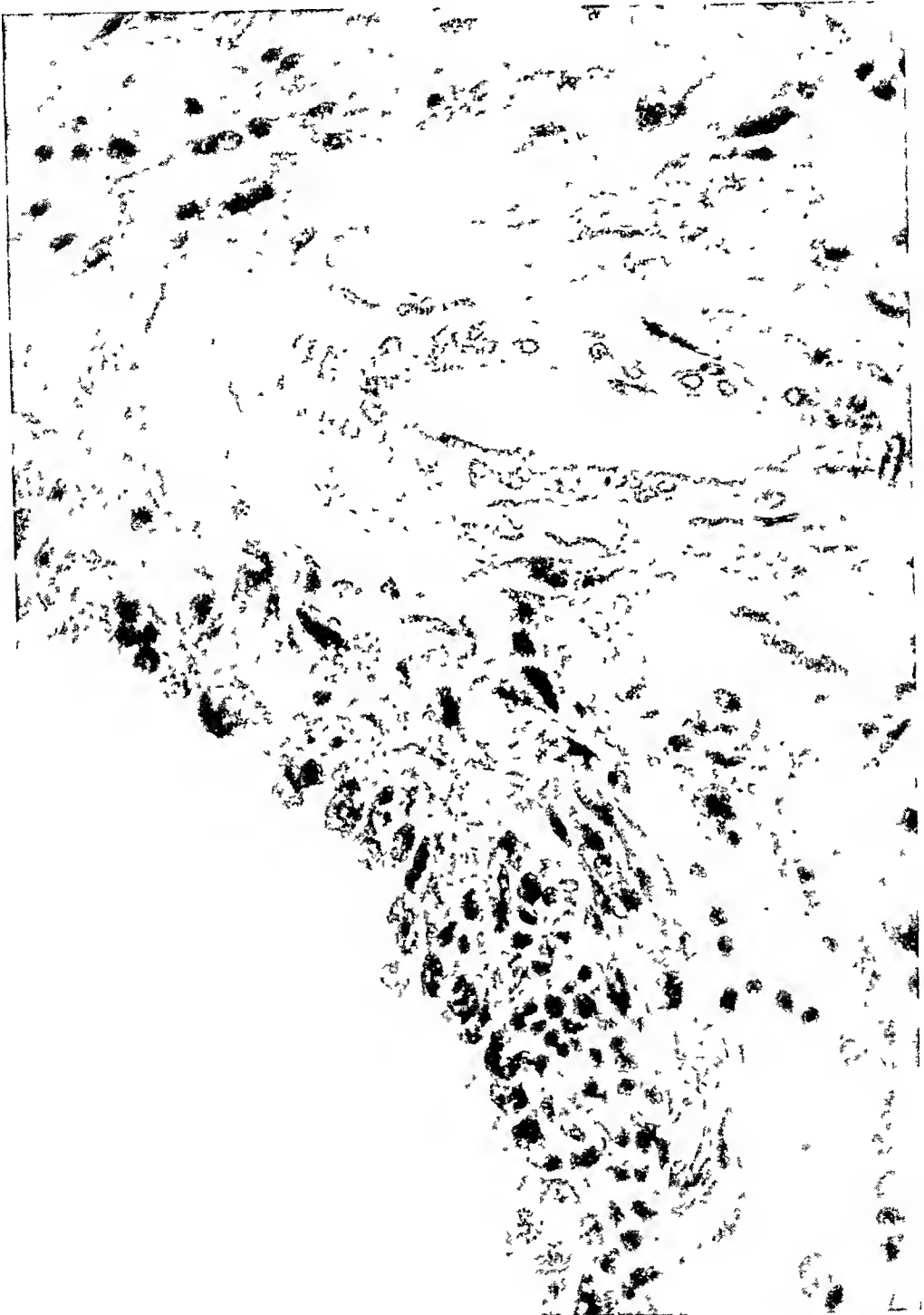


FIG 4. High power photomicrograph of parietal pleura and adhesion showing mesothelial swelling and proliferation, edema, and leukocytic infiltration with well formed blood vessel  $\times 500$  (Courtesy of the Army Medical Museum.)

was greatly improved and he seemed to be making a satisfactory recovery from his shock until about 6 p.m., when he suddenly again became very restless and breathless. He rapidly went into profound shock and died 15 minutes later.

*Autopsy.* At the necropsy about 2000 c.c. of fluid blood were found in the left thoracic cavity and the mediastinum was pushed to the right of the midline approximately three inches. The left lung was completely collapsed but was adherent to the left apex by dense adhesions. Three thick cord-like bands from 2 to 4 mm. in diameter were found firmly adherent to the parietal pleura and there were several tough adhesive tags present over the lateral and posterior aspects of the left pulmonary apex. When the adhesive bands between the parietal pleura and apex were severed, it was observed that some small interstitial hemorrhages were present in the adhesions and in the thickened fibrous pleura immediately surrounding these bands. A careful examination of the vascular supply of the lung showed nothing abnormal. There was one small subpleural calcified nodule in the left apex about 3 mm. in diameter. Careful search revealed no evidence of active tuberculosis. The right lung was entirely negative, and the remaining viscera showed no lesions except for a Chiari network in the right cardiac auricle and a mild degree of atheromatous change in the coronary arteries.

*Histopathology.* Microscopic examination of the viscera showed nothing of importance with the exception of the findings in the left lung and its apical adhesions. The left lung showed thickening of the pleura over most of the upper lobe with prominence of the mesothelial layer, and the underlying alveoli contained many phagocytes laden with brown pigment.

Sections through the visceral pleura abutting upon the adhesions revealed marked prominence and some desquamation of swollen serosal mesothelial cells. Considerable fibrin and white cells were found about the adhesions (figure 1). Higher magnification brought out the pleural thickening and the mesothelial swelling quite strikingly; and also the presence of a moderate infiltration of leukocytes along with some fibrin in the subserosal stroma (figure 2).

Various sections taken through the parietal pleura and the attached adhesive bands again showed the same swollen layer of surface mesothelial cells near the attachment of the adhesions and on the surface thereof. In the adhesions, leukocytes, red cells, fibrin and edema were observed in the subendothelial stroma (figure 3). Under higher power the parietal pleura with its adhesions again showed swelling and proliferation of the mesothelium. Moreover, a well developed vascularity was encountered in many sections of the adhesions, both parietal and visceral (figure 4).

## DISCUSSION

An examination of the important features of the foregoing case and a study of similar reports in the literature would suggest that the deceased, five days previous to his admission to the hospital, might have torn the well vascularized left, apical, pleural adhesions following the exertion of throwing a heavy bag over his left shoulder. This rupture possibly produced slow bleeding into the left thorax. The patient's symptoms also suggest that the pneumothorax occurred at 2 a.m. on the morning of his hospital admission. It is also hypothesized that the collapse of the left lung might have increased the bleeding from the ruptured adhesions which produced the picture of rapidly developing hemopneumothorax and shock.

In a review of the literature, we found 13 cases of spontaneous hemopneumothorax which came to necropsy and the important clinical and autopsy findings are summarized in the following chart (chart 1).

CHART I

Clinical Findings										Autopsy Findings					
Name and Date	Sex and Age	Nationality and Occupation	Outstanding Clinical Findings	Duration in Days	Side Involved	Past History and Possible Contributory Etiology	Chest X-ray	Aspiration of Blood	Blood Transfusion	Quantity and Character of Blood in Chest	Apical Scars	Bullae	Adhesions	Microscopic Examination	Comments
1. Pitt <sup>3</sup> 1900	♂ 18	Eng. Not given	Gradual development pain right shoulder and chest. First seen in shock.	2	Rt.	5 days previously sore throat and vomiting.	0	+	0	Fluid 4½ L.	0	One apical	1	0	Ruptured adhesion attached to apical bulla.
2. Rolleston <sup>3</sup> 1900	♂ 21	Eng. Not given	Sudden pain right upper quadrant radiating to shoulder. Shock. Diagnosed perfr. ulcer.	8	Rt.	None	0	+	0	Fluid 2 L. Few clots	0	0	0	0	No bleeding point found.
3. Fischer <sup>4</sup> 1922	♂ 22	German Cinema techn.	Sharp pain right chest. Wk. later pain right upper quadrant. Shock. Laparotomy for perfr. ulcer.	7	Rt.	Cough for one year.	0	+	0	Coagulated 4½ L.	+	Many bifat. apical	0	+	Fresh blood oozed from ruptured bulla.
4. Kafer <sup>4</sup> 1923	♂ 30	Danish Rifleman	Knife-like pain in neck and between shoulder blades. Signs of pneumothorax and fluid.	3	Lt.	Fell from bicycle 2 mo. previous. Struck rib. Severe cold 1 wk.	0	+	0	Not mentioned	0	0	0	0	No lesions lung or pleura.
5. Horsden 1931 and Piggott <sup>5</sup>	♂ 44	Eng. Plumber	Severe pain left chest and abdomen. Over period of 4 days developed signs of internal hemorrhage and shock.	4	Lt.	Winter cough for 7 years with pain lt. chest.	0	0	0	Coagulated 1 L.	+	2	2	0	Tough adhesions torn from chest wall.
6. Tait and Wakely <sup>7</sup> 1935	♂ 32	Eng. Sedentary occ.	Pain in chest growing worse over period 4 days with signs of pneumothorax and fluid.	8	Rt.	Lifted end of bed.	0	+	0	Fluid 2½ pts. Not coagulated	0	12 Near apex	0	0	Perforated bulla filled with fresh blood.
7. Rossel <sup>8</sup> 1935	♂ 20	French Soldier	Sudden pain in back with signs of intrapleural hemorrhage and shock.	9	Rt.	Previous roentgen-ray chest negative.	+	+	+	Fluid 3½ L.	0	Several bifat.	0	+	Bilateral pneumothorax. Origin left. Hemothorax not found.

CHART I—Continued

Clinical Findings										Autopsy Findings					
Name and Date	Sex and Age	Nationality and Occupation	Outstanding Clinical Findings	Duration in Days	Side Involved	Past History and Possible Contributory Etiology	Chest X-ray	Aspiration of Blood	Blood Transfusion	Quantity and Character of Blood in Chest	Apical Scars	Bullae	Adhesions	Microscopic Examination	Comments
8. Davidson <sup>9</sup> 1935	♂ 28	Eng. Clerk	On admission signs of intra-pleural fluid with dyspnea and anemia.	21	Rt.	3 wks. prior to admission sudden pain in chest while walking.	0	+	+	Fluid 4 L.	Lt.	0	Lt. apex only	0	No lesion on right except collapsed lung.
9. Davidson <sup>10</sup> 1935	♂ 26	Eng. Tailor	1 day prior to admission sudden pain in right chest with collapse. Admitted in shock.	2	Rt.	None	0	0	0	Fluid 3.2 L.	No	Sev. apical	Both apical	+	Torn adhesions between lung and pericardium. Very vascular.
10. Jones and Gilbert <sup>11</sup> 1936	♂ 23	Amer. Law Student	Knife-like pain lower right chest and upper belly, with signs of pneumothorax and fluid.	38	Rt.	Similar pain to present, 2 wks. and 3 mos. previously.	+	+	+	Fluid blood 4 L. Free fibrin 750 c.c.	Lt.	1	0	+	Bulla not ruptured. Bleeding source not found.
11. Louriau <sup>12</sup> 1938	♂ 22	Amer. Barber	Sudden pain in chest with dyspnea. Signs of effusion and anemia.	4	Lt.	Acute intermittent cough.	0	+	+	Not stated	+	1 Lt. Sev. Rt.	+	0	Ruptured apical bulla. Bleeding source not found.
12. Davidson 1940 and Simpson <sup>13</sup>	♂ 26	Eng. Soldier	Sudden pain in chest with signs of effusion and rigid belly.	2	Rt.	Following military parade.	0	+	+	2½ L. Fluid and clots	+	1	+	+	Ruptured apical bulla. Vascular torn adhesions at base right.
13. Lorge <sup>14</sup> 1940	♂ 34	Amer. Messenger	Sudden pain in chest followed in few hours by shock.	1	Lt.	Chest pain 2 mos. previously. Fell on back 6 wks. previously.	+	+	0	Fluid 3 L. Few clots	Rt. and Lt.	Few	0	0	Bleeding point not found.
14. Hejwlg and Schmidt 1945	♂ 30	Amer. Naval Officer	5 days previously sharp pain in chest. 7½ hrs. prior to admission sudden pain followed by shock.	1	Lt.	Slung bag over left shoulder.	+	+	+	Fluid 2 L.	+	0	+	+	3 torn cord-like bands torn from parietal pleura.

Hartzell<sup>1</sup> enumerated 14 cases of spontaneous hemopneumothorax that came to autopsy. A careful examination of his references, however, revealed that the case reported by Perry<sup>14</sup> in 1938 was apparently the same one Davidson<sup>9</sup> had published in 1935. In 1936 Birch<sup>15</sup> discussed a fatal case of spontaneous hemopneumothorax which was complicated by a miniature tuberculous cavity at the apex of the right lung which cavity had not ruptured. Moreover, there was no other evidence of tuberculosis. The right pleural cavity contained several pints of fluid blood and some air. No emphysematous blebs were present and on the anterior aspect of the right upper lobe, an area of roughened pleura was observed, and the escape of air and blood into the chest cavity apparently had its origin here. Neither gross nor microscopic examination, however, revealed any changes of interest. The left lung and remainder of the body were quite normal. This case is given in some detail because it would have been included in the above table had it not been for the minute tuberculous cavity.

An analysis of figure 5 reveals that all of the subjects were males between the ages of 18 and 44. Unusual strain, exertion, or trauma did not seem to be factors in the etiology of the condition and there was nothing significant in the past histories or occupations of the victims. In most instances the first symptoms of acute, sharp, chest pain appeared when the patient was quiet and the onset was not infrequently accompanied by severe, abdominal pain and even rigidity. This latter manifestation was very striking in some cases, so much so in fact that perforated peptic ulcer was diagnosed and, in one instance, an exploratory laparotomy was performed. The duration of symptoms until death ranged from one to 38 days. The right chest was more frequently involved than the left, and the diagnosis of hemothorax was established by aspiration of blood from the affected chest in all but two cases. Removal of air and blood from the thorax and blood transfusions were the only therapeutic measures of importance that were employed.

At necropsy the quantity of blood found in the chest varied from one to four and one-half liters and in most instances the blood was either unclotted or contained only a few clots. In the majority of cases apical pleural scars were observed and in six cases adhesions were found on the involved lung. Emphysematous bullae were observed 10 times, ruptured bullae four times and torn pleural adhesions five times. Microscopic examination of the adhesions in two cases revealed them to be highly vascular. The source of the bleeding was not found in half of the cases. In many instances the origin of pneumothorax was not ascertained, whereas, in three cases, no lesions of the collapsed lung could be discovered.

### CONCLUSIONS

1. A case of fatal spontaneous hemopneumothorax with necropsy is reported. The intrapleural bleeding appeared to have arisen from torn apical vascular adhesions.

2. An outline of the pertinent facts in the reported fatal cases of the above condition is given and what were considered the significant clinical and pathological data are briefly discussed.

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## EDITORIAL

### GOLD SALTS FOR RHEUMATOID ARTHRITIS

HAVING returned to many professional and economic changes, the homecoming medical officer will have unfortunately found one condition relatively unchanged; namely, the frustrating problem of rheumatoid arthritis. He will also find still continuing and still unsettled, the prewar controversy over the use of gold salts for rheumatoid arthritis.

Why are the opinions of internists and specialists concerning this treatment so diverse after twenty years of use? Gold salts were first employed for rheumatoid arthritis in Germany about 1927 by physicians who, impressed with results in tuberculosis, regarded rheumatoid arthritis as related to tuberculosis, an unproved untenable notion. First American reports appeared in 1936. During the 15 prewar years thousands of patients who had rheumatoid arthritis were treated and many European and American reports appeared. Most reports strongly favored chrysotherapy but several drawbacks were admitted: not all patients were benefited thereby; many developed relapses; toxic reactions were frequent and occasionally fatal.

Despite the empiric nature of this treatment and the danger inherent therein many physicians of wide experience and mature judgment concluded that gold salts provided "the best single remedy" ever found for this serious disease, and that chrysotherapy deserved further investigation. It was hoped that nontoxic preparations could be developed, that the mode of action of gold salts could be discovered, that more successful schemes of dosage could be evolved, that tests of susceptibility to, or remedies to control, gold intoxication could be devised. To what extent have these hopes been realized since 1942?

Reports of results in more than 2,000 additional American cases and in at least 1,000 foreign cases have appeared.<sup>1, 2, 3, 4, 5</sup> Results varied rather widely: From 6 to 54 per cent of the patients became free of symptoms and more frequently from 10 to 15 per cent obtained "arrests." In an additional 35 to 65 per cent of cases marked improvement was noted. Thus in general about 50 to 60 per cent of patients became symptom-free or were notably relieved.

Of special interest is the three to five year follow-up study of 142

<sup>1</sup> CECIL, R. L., KAMMERER, W. H., and DEPRUME, F. J.: Gold salts in the treatment of rheumatoid arthritis; a study of 245 cases, *Ann. Int. Med.*, 1942, xvi, 811-827.

<sup>2</sup> COHEN, A., GOLDMAN, J., and DUBBS, A. W.: The treatment of rheumatoid arthritis with 417 courses of gold; an analysis of 259 cases, *New England Jr. Med.*, 1945, ccxxxiii, 199-203.

<sup>3</sup> GARDNER, E. R.: The use of gold in rheumatoid arthritis, *Med. Rec.*, 1941, cliii, 321-323.

<sup>4</sup> HARTUNG, E. F.: The treatment of rheumatoid arthritis including gold salts therapy, *Bull. New York Acad. Med.*, 1943, xix, 693-703.

<sup>5</sup> SUNDELIN, F.: Die Goldbehandlung der chronischen Arthritis unter besonderer Berücksichtigung der Komplikationen, *Acta med. Scandinav.*, 1941 (Supp.), cxvii, 1-291.

patients by Ragan and Tyson<sup>6</sup>: 11 per cent were not improved, 76 per cent were improved, and in the remaining 13 per cent complete remissions were obtained; "five year cures" occurred in 6 per cent. Relapses occurred in 75 per cent but 80 per cent of those who relapsed improved under further treatment.

These recent reports are conservative but the results approximate closely those noted between 1927 and 1940. One particular lack has been apparent, the matter of controls. In 1940 Ellman, Lawrence and Thorold<sup>7</sup> obtained remissions in 47 per cent of patients given weekly doses of 200 to 300 mg. of gold salts, in 27 per cent of those given 100 mg. and in only 3 per cent of a control series given injections of sterile almond oil. Recently Fraser,<sup>8</sup> conducting a "blindfold test," noted marked improvement in 42 per cent of patients given gold, in only 8 per cent of patients injected with an inactive control substance prepared to look like the solution of gold. Toxic reactions affected 75 per cent of patients receiving gold, but 37 per cent of the control group experienced rashes, and so forth which had been regarded as "toxic reactions."

Results have been generally better in the earlier stages of the disease.<sup>1,3</sup> But the disease in many late cases has responded favorably and in some early cases has been refractory.

Originally the amounts of gold injected as a single dose were quite great but they were gradually reduced so that until recently the standard maximal individual doses given in the United States and Great Britain were generally 100 mg. of gold salts (about 50 mg. of gold). But after careful observations Smyth and Freyberg<sup>9</sup> concluded that the optimum maximal dose was 50 mg. of gold salts (about 25 mg. of gold). Such doses were as effective as the larger ones but 25 mg. doses of gold salts were considered insufficient except in mild cases among adults or for children. But others<sup>10</sup> using maximal doses of 25 mg. of gold salts recently reported marked improvement in 53 per cent of their cases, complete remissions in none. Hence the merits of the "smaller dose program" have yet to be determined.

No special merit applies to any one of the numerous gold compounds commercially available. For reasons to be noted hereafter some preparations are less toxic, but less effective, than others.

Even though many patients are notably benefited or even completely relieved, a disturbingly high percentage of relapses develop. Often the gold-induced remissions lasted many months or for two years or so, but the

<sup>6</sup> RAGAN, C., and TYSON, T. L.: Chrysotherapy in rheumatoid arthritis; a three-year study of 142 cases, *Am. Jr. Med.*, 1946, i, 252-256.

<sup>7</sup> ELLMAN, P., LAWRENCE, J. S., and THOROLD, G. P.: Gold therapy in rheumatoid arthritis, *Brit. Med. Jr.*, 1940, ii, 314-316.

<sup>8</sup> FRASER, T. N.: Gold treatment in rheumatoid arthritis, *Ann. Rheumat. Dis.*, 1945, iv, 71-75.

<sup>9</sup> SMYTH, C. J., and FREYBERG, R. H.: Experiences with gold salts in the treatment of rheumatoid arthritis, *Univ. Hosp. Bull., Ann Arbor*, 1941, vii, 45-47.

<sup>10</sup> RAWLS, W. G., GRUSKIN, B. J., RESSA, A. A., DWORZAN, H. J., and SCHREIBER, D.: Analysis of results obtained with small doses of gold salts in the treatment of rheumatoid arthritis, *Am. Jr. Med. Sci.*, 1944, ccvii, 528-533.



relapse rate has varied from 12 to 75 per cent depending on the duration of the studies.

If the foregoing summarized the story of chrysotherapy for rheumatoid arthritis there would be almost unanimous approval and widespread use of this remedy but, unhappily, toxic reactions still provide a great drawback. The incidence of toxic reactions recently has varied from as low as 8 per cent<sup>3</sup> to as high as 75 per cent,<sup>8,11</sup> these differences depending partly on the activity or relative inertness of the gold preparation used and partly on what the various writers considered to be reactions worthy of note. Most writers noted toxic reactions of some sort in about 40 per cent of patients treated. The reactions were generally mild and transient. In about 3 to 11 (average about 5) per cent of cases reactions were serious (exfoliative dermatitis, agranulocytosis, thrombocytopenic purpura, acute enterocolitis, hepatitis) but were nonfatal.

A few reactions proved fatal but fatal reactions are occurring with increasing rarity. Mortality rates from chrysotherapy, as high as 3 per cent in 1935, and prior to 1939 between 0.5 and 0.6 per cent,<sup>11,12</sup> have recently been between 0.38 and 0.43 per cent.<sup>1,2,4,6</sup> Deaths occurred from acute enterocolitis, cerebral purpuric hemorrhages, thrombocytopenic purpura or aplastic anemia. Agranulocytosis, the cause of several deaths in previous years, is now controllable by penicillin.<sup>13,14</sup> Several physicians have used chrysotherapy with no fatalities in small series of from 30 to 100 cases but with wider experience they may also note an occasional fatality.

Occasionally toxic reactions appear early during treatment and probably represent hypersensitivity to gold. But most reactions occur later, after a few hundred milligrams of gold salts have been given: such reactions represent metallic protoplasmic poisoning. Thus most toxic reactions have been related to the accumulated total of individual doses.

Many attempts have been made to prevent reactions by using "gold sensitivity tests" (patch tests or preliminary injections at two day intervals of minute doses of gold) or by the administration, during chrysotherapy, of various vitamins, calcium preparations, liver extracts or bile salts. But statistical evidence having indicated their ineffectiveness, practically all American and British workers have agreed that there is no known way of preventing toxicity. One European pioneer in the use of gold salts stands almost alone in his continuing belief that practically all serious toxic reactions can be prevented by a preliminary period of intensive vitamin therapy.<sup>15</sup>

<sup>11</sup> SHORT, C. L.: Gold therapy of rheumatoid arthritis, *Bull. New England Med. Center*, 1942, iv, 31-34.

<sup>12</sup> SASHIN, D., SPANBOCK, J., and KLING, D. H.: Gold therapy in rheumatoid arthritis, *Jr. Bone and Joint Surg.*, 1939, n.s. xxi, 723-734.

<sup>13</sup> BOLAND, E. W., HEADLEY, N. E., and HENCH, P. S.: The treatment of agranulocytosis with penicillin, *Jr. Am. Med. Assoc.*, 1946, cxxx, 556-559.

<sup>14</sup> BOLAND, E. W., HEADLEY, N. E., and HENCH, P. S.: The treatment of agranulocytosis with penicillin: report of a case resulting from chrysotherapy for rheumatoid arthritis, *Proc. Staff Meet., Mayo Clin.*, 1946, xxi, 197-206.

<sup>15</sup> SECHER, K.: Directions for the treatment of rheumatic joint diseases with sanocrysin and physical therapy, Copenhagen, Andr. Fred. Hst. & Son, 1946, 56 pp.

Once toxic reactions have occurred, until very recently there has been no known rapid control thereof as they usually continued until an appreciable amount of the injected gold was excreted. Treatment was entirely symptomatic. But recent results with the use of BAL (British Anti-Lewisite) lead us to hope that an effective method for controlling at least some of the serious toxic reactions may be at hand. Nine patients who had exfoliative dermatitis of less than two months' duration, one patient who had severe thrombocytopenic purpura and one who had granulocytopenia, responded rapidly to the intramuscular injections of BAL.<sup>16-18</sup> One patient whose dermatitis has been present for three months was not relieved. Although the number of patients so treated is as yet too small to be conclusive these preliminary results are indeed promising. Despite this new approach to the treatment of toxic reactions the best way to minimize them is to spot them, if possible, in their incipency and stop the injections immediately, but sometimes only temporarily. To this end frequent clinical and laboratory observations are mandatory. Thus impending skin reactions or blood dyscrasias, the two most troublesome toxic manifestations, may be discovered and treated early.

Were the mode of action of gold salts in rheumatoid arthritis known, the variations in results and in toxicity and the cause for relapses might be explained. Gold salts have certain bacteriostatic and chemotherapeutic properties. But since no bacterial cause of rheumatoid arthritis has been found, these observations do not necessarily apply.

More fruitful than bacteriologic studies have been the investigations of Freyberg, Hartung and their colleagues<sup>9, 19, 20, 21, 22</sup> on the metabolism of gold compounds in the human body. Injected gold salts are dispersed via plasma and deposited in various organs and tissues, chiefly liver and kidneys, from whence they are eliminated (by urine and feces) so slowly that weekly injections build up significant concentrations in plasma and tissues. Thus 75 to 85 per cent of the gold serially injected remains in the body. Significant amounts of gold may be still present in plasma for eight to ten months

<sup>16</sup> COHEN, A., GOLDMAN, J., and DUBBS, A. W.: The treatment of acute gold and arsenic poisoning; use of BAL (2,3-dimercaptopropanol, British Anti-Lewisite), *Jr. Am. Med. Assoc.*, 1947, cxxxiii, 749-752.

<sup>17</sup> LOCKIE, L. M., NORCROSS, B. M., and GEORGE, C. W.: Treatment of two reactions due to gold; response of thrombopenic purpura and granulocytopenia to BAL therapy, *Jr. Am. Med. Assoc.*, 1947, cxxxiii, 754-755.

<sup>18</sup> RAGAN, C., and BOOTS, R. H.: The treatment of gold dermatitides; use of BAL (2,3-dimercaptopropanol), *Jr. Am. Med. Assoc.*, 1947, cxxxiii, 752-754.

<sup>19</sup> BLOCK, W. D., and KNAPP, E. L.: Metabolism, toxicity and manner of action of gold compounds in the treatment of arthritis. VII. The effect of various gold compounds on the oxygen consumption of rat tissues, *Jr. Pharmacol. and Exper. Therap.*, 1945, lxxxiii, 275-278.

<sup>20</sup> FREYBERG, R. H.: Recent trends in the treatment of rheumatoid arthritis, *Ohio State Med. Jr.*, 1942, xxxviii, 813-820.

<sup>21</sup> FREYBERG, R. H., BLOCK, W. D., and WELLS, G. S.: Gold therapy for rheumatoid arthritis; considerations based upon studies of the metabolism of gold, *Clinics*, 1942, i, 537-570.

<sup>22</sup> HARTUNG, E. F., COTTER, J., and GANNON, C.: The excretion of gold following the administration of gold sodium thiomalate in rheumatoid arthritis, *Jr. Lab. and Clin. Med.*, 1941, xxvi, 1750-1755.

after the completion of a "course" in which weekly doses are of 100 mg. of gold salts, for three to five months when 50 mg. is used, for about one month when 25 mg. is used. Gold has been detected in urine 30 to 600 days after the last injection has been given.

All gold compounds are not metabolized similarly. Colloidal gold, deposited chiefly in liver and spleen, is generally quickly phagocytosed by reticulo-endothelium; hence, colloidal gold preparations are generally ineffective therapeutically.

Some workers have concluded that the toxic and therapeutic properties of gold salts are probably largely inseparable; the more harmless a preparation is the less effective it may be. Perhaps gold, by altering the metabolism of certain cells, inhibits an enzyme system a disturbance of which is primarily responsible for rheumatoid arthritis.<sup>6, 19</sup> Perhaps the ameliorating effect of gold in rheumatoid arthritis is analogous to, if not basically identical with, that induced by intercurrent jaundice or pregnancy.<sup>23</sup>

Although many European physicians continue to give doses of gold salts many times greater than 50 or even 100 mg.<sup>15</sup> most American physicians have abandoned the former "course method." To reduce the incidence of toxic reactions and of relapses, maximal weekly doses of 50 mg. of gold salts are now generally used and when articular symptoms abate and sedimentation rates approach normal, the doses are not discontinued but small maintenance doses are continued for several months.<sup>6, 20, 24</sup>

Let us now weigh the arguments for and against chrysotherapy. The "balance sheet" shows that currently a patient so treated has about a 10 to 15 per cent chance of obtaining a "complete remission" lasting from several months to an undetermined number of years, about a 50 per cent additional chance of being notably improved, about a 35 per cent chance of obtaining no significant relief. On the other side of the ledger he has a 50 per cent chance of having no toxic reaction, a 45 per cent chance of having a minor or moderate reaction, a 3 to 5 per cent chance of a serious but nonfatal toxic reaction, and about one chance in 250 (0.4 per cent) of developing a fatal reaction (unless the use of BAL lessens these chances).

The protagonists of chrysotherapy admit that gold salts are dangerous and that physicians giving them are (or should be) "in a constant state of alarm." Despite this, chrysotherapy is superior to any other treatment and is the only method which will markedly change the course of the disease in a significant percentage of cases. To call it the best single agent "does not appear to be a sensational statement when one considers how disappointing most other remedies usually are."<sup>24</sup> Rheumatoid arthritis, the greatcrippler, produces human wastage of much social and economic importance. Always potentially serious, it represents "big game" and cannot be fought

<sup>23</sup> HENCH, P. S.: The advantages of hepatic injury and jaundice in certain conditions, notably the rheumatic diseases, *Med. Clin. North America*, 1940, xxiv, 1209-1237.

<sup>24</sup> CECIL, R. L.: The problem of dosage in the administration of gold salts for rheumatoid arthritis, *Med. Clin. North America*, 1946, xxx, 545-552.

with small caliber weapons. When defensive warfare (use of general measures) is obviously failing, the aggressive application of total offensive war (chrysotherapy) is, despite its risks, justified by the vicious nature of rheumatoid arthritis.

The critics <sup>11, 25</sup> of chrysotherapy properly point out that very few (only two?) control studies have been made; most workers have reported only the "early results" tabulated a few months after the last injection; only a few long time results have been reported. Many reports are difficult to evaluate because their authors have "lumped together 'cures' and 'improvements' to make an impressive showing," have failed to state their criteria for judging results and have failed to classify results in relation to the stage and activity of the disease. The tremendous psychic value of chrysotherapy must be taken into account.

Rheumatoid arthritis is potentially reversible as shown by the fact that many patients are only briefly affected, and those chronically affected may be temporarily "cured" by jaundice or pregnancy. This potential reversibility must not be lost sight of. One critical observer <sup>11</sup> has claimed results from "general measures" (the disease "arrested" in 16 per cent, notably affected in 50 per cent more) equal to or better than those from chrysotherapy. The toxicity inherent in chrysotherapy makes it unsuitable for use by average practitioners without special experience. Gold salts are not constantly effective, are not specific, are at best a palliative and have not been proved to be a necessary adjunct to routine measures.

A strong counterargument is that gold may well accomplish in six months or less what nature or general measures may take six years to accomplish. Surgeons and patients do not hesitate to accept the risks of cholecystectomy or hysterectomy to relieve symptoms much more bearable than those of progressive rheumatoid arthritis. Yet the mortality rates of such procedures are as great or several times greater than that of chrysotherapy. In view of all the foregoing the use of gold salts seems entirely justified (1) in cases of progressive rheumatoid arthritis unrelieved by a reasonable but not too long a period of older and safer methods of treatment, (2) when the patient clearly understands and accepts the risk and (3) when the physician is in a position to give the treatments with the necessary clinical and laboratory safeguards.

Two recent incidents impressed the writer. A visiting physician said "I wish I could use gold but if I did and something happened I'd be run out of town." On another occasion the writer seeing a farmer's wife with progressive rheumatoid arthritis unrelieved by much therapy, told her frankly of the merits and risks of gold injections. The husband spoke up: "You won't give that to my wife and run the risk of killing her. She can't do much but I need her on the farm anyhow." The wife was silent for a minute. Then tears appeared on her cheeks. Turning to her husband and

<sup>25</sup> STEINBROCKER, O.: Therapeutic results in rheumatoid arthritis, Jr. Am. Med. Assoc., 1946, CXXXI, 189-193.

laying a hand on his knee she said quietly, "But John, I'm the one who lies awake in pain week after week. I'm the one who takes the risk. I want to try it."

Thus it appears that to such a venture there are four interested parties (in the order of importance): (1) the patient who takes the chief risk; (2) the physician who risks his peace of mind but probably not his "reputation"; (3) the interested bystanders, chiefly the close relatives, and (4) the community which if enlightened wants no arthritic derelicts as economic liabilities and is certainly sympathetic to the conscientious physician even in his failures. The distressed rheumatoid patient cannot be objective; in desperation he will try anything. Such an attitude does not absolve the physician of his responsibility, rather it enhances it and requires that the physician shall have fully acquainted himself with chrysotherapy either by assiduous reading or preferably by an adequate visit to one of the clinics using such treatment. It is certainly desirable and, by the proper explanations, usually possible to obtain the understanding, if not the approval, of the interested bystanders. When the latter is not forthcoming it is still the right of the afflicted patient and his physician coöperatively to assume the responsibility.

PHILIP S. HENCH

## REVIEWS

*Agnosia, Apraxia, Aphasia. Their Value in Cerebral Localization.* 2nd Edition, revised. By J. M. NIELSEN, M.D., F.A.C.P., Assisted by J. P. FITZGIBBON, M.D. 292 pages; 24 × 16 cm. Paul B. Hoeber, Inc., New York. Price, \$5.00.

This monograph on the most complex aspect of clinical neurology not only presents a well integrated analysis of the subject, but also interprets the data in a manner that gives them diagnostic significance. However, the highly technical nature of the subject would make it difficult for anyone who is not a trained neurologist to apply the detailed information made available.

The entire field of agnosia, apraxia and aphasia is covered thoroughly on the basis of selected cases from a vast literature, and the authors' own clinical and pathological material. Without sacrificing any of the dynamic aspects of cerebral cortex function, the authors have been able to correlate the clinical and pathological data so as to give the latter significant value in cerebral localization. The methods used in arriving at conclusions are clearly portrayed; and they are both theoretically sound and clinically applicable.

A concise and lucid summary is provided in the appendix; and the authors' terminology is correlated with older nomenclature wherever possible, thus affording a basis on which earlier literature can be interpreted in the light of their own concepts.

H. A. T.

*The Diagnosis and Treatment of Bronchial Asthma.* By LESLIE N. GAY, Ph.B., M.D., Assistant Professor of Medicine of the Johns Hopkins University School of Medicine, Director of the Allergy Clinic of the Johns Hopkins Hospital. Foreword by WARFIELD T. LONGCOPE, A.B., M.D., Professor of Medicine of the Johns Hopkins University School of Medicine, Physician-in-Chief of the Johns Hopkins Hospital, Baltimore. 334 pages; 24 × 16 cm. Williams and Wilkins, Baltimore, Maryland. Price, \$5.00.

The author divides the subject of bronchial asthma into seven chapters presented in the following order: the physiology of normal respiration and the asthmatic state; etiology; pathology; diagnosis; complications and differential diagnosis; psychosomatic paroxysms and, lastly, the treatment of the condition.

The book is clearly printed and well arranged. The diagrams and pictures are excellent and beautifully reproduced. They are a distinct addition to the text.

The subject matter reflects the author's wide experience and sound clinical judgment.

It seems to this reviewer that too much space has been allotted to the discussion of the rather elementary subject of pollens and pollen counts in a book designed to cover in detail the whole subject of asthma. Further, the classification of asthma offered, covering as it does over two full pages and consisting of some 45 subdivisions, seems too involved and may tend to complicate rather than clarify for the physician an already confusing subject.

The sections on pathology, diagnosis and treatment are excellent and the one on psychosomatic factors is particularly worthy of consideration as directing attention toward a much neglected phase of the subject. The part played by sinus infection in the etiology of asthma is well presented. A valuable feature in this monograph is the discussion of the use of radium in eradicating nasopharyngeal lymphoid tissue infection, as suggested by Crowe and, applied therapeutically by his and the author's

clinics. It is revolutionary in the therapy of asthma. No one interested in asthma can afford not to avail himself of this book.

H. M. B.

*Office Endocrinology.* Third Edition, revised and enlarged. By ROBERT B. GREENBLATT, B.A., M.D., C.M. 303 pages; 23.5 × 15.5 cm. 1947. Charles C. Thomas, Springfield, Ill. Price, \$4.75.

This new and revised edition is better arranged than previous ones, is readily readable and well up to date. The two new chapters on the relation between the endocrine, vegetative-nervous and hypothalamico-pituitary systems are too brief to accomplish more than stimulation of interest. The chapter on the mechanism of uterine bleeding is an excellent presentation of this subject in a short space. The entire book is characterized by an absence of extraneous material. The increasing importance of the use of progesterone in endocrine therapy is well brought out. However, only brief mention is made of the gonadotropic hormones. The physician who has some basic knowledge of endocrinology will find this book an interesting and valuable addition to his library. The average practitioner will find recommended methods of therapy too complex and not sufficiently well defined to be of much practical value.

R. E. B.

*Skin Disease in Children.* By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia University, and ANTHONY C. CIPOLLARO, M.D., Associate in Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia University. 448 pages; 24 × 16 cm. 1946. Paul B. Hoeber, Inc., New York and London. Price, \$7.50.

This text adequately presents the subject of skin diseases in children. The subject matter is presented in a way to make it of value to the student of dermatology as well as to the practitioner of pediatrics. There are a number of good illustrations of the more common conditions. The first chapter, on the care of the skin, is excellent. In the opinion of the reviewer such a chapter should be included in the larger texts on general dermatology. The authors state that acne vulgaris and leprosy have been included in the chapter on pyogenic conditions for convenience, but it is difficult to understand why, as neither of these conditions is basically related to pyogenic bacteria. Throughout the text the authors stress the importance of diagnosis prior to the institution of therapy. The various diagnostic aids are thoroughly reviewed. The chapter on syphilis in children by Dr. Herman Beerman is excellent. Physicians who treat children will find this monograph a valuable reference.

H. M. R., JR.

### BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Modern Dermatology and Syphilology.* Second Edition. By S. WILLIAM BECKER, M.D., and MAXIMILIAN E. OBERMAYER, M.D. 1017 pages; 26 × 18.5 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, \$18.00.

- The Treatment of Diabetes Mellitus.* Eighth Edition, revised. By ELLIOTT P. JOSLIN, A.M., M.D., Sc.D., HOWARD F. ROOT, M.D., PRISCILLA WHITE, M.D., ALEXANDER MARBLE, A.M., M.D., and C. CABELL BAILEY, M.D. 861 pages; 24 × 15 cm. 1947. Lea & Febiger, Philadelphia. Price, \$10.00.
- The Chemical Kinetics of the Bacterial Cell.* By C. N. HINSHELWOOD, R.R.S. 284 pages; 24.5 × 16 cm. 1947. Oxford University Press, New York. Price, \$6.75.
- Tratado de Patologia Digestiva.* By C. BONORINO UDAONDO and M. R. CASTEX. 1297 pages; 26.5 × 17 cm. 1946. Lopez & Etchegoyen, S.R.L., Buenos Aires.
- Tumores y Seudotumores de la Mama.* By JACINTO MORENO, M.D. 142 pages; 23 × 16 cm. 1946. Lopez & Etchegoyen, S.R.L., Buenos Aires.
- Office Endocrinology.* Third Edition, revised and enlarged. By ROBERT B. GREENBLATT, B.A., M.D., C.M. 303 pages; 23.5 × 15.5 cm. 1947. Charles C. Thomas, Springfield, Ill. Price, \$4.75.
- Practical Physiological Chemistry.* Twelfth Edition. By PHILIP B. HAWK, Ph.D., BERNARD L. OSER, Ph.D., and WILLIAM H. SUMMERSON, Ph.D. 1323 pages; 23.5 × 16 cm. 1947. The Blakiston Company, Philadelphia. Price, \$10.00.
- The Preservation of Proteins by Drying.* Special Report Series. By R. I. N. GREAVES. 54 pages; 24.5 × 15 cm. 1946. His Majesty's Stationery Office, London. Price, 60 cents.
- The Cultivation of Viruses and Rickettsiae in the Chick Embryo.* Special Report Series. By W. I. B. BEVERIDGE and F. M. BURNET. 92 pages; 24.5 × 15 cm. 1946. His Majesty's Stationery Office, London. Price, 60 cents.



# COLLEGE NEWS NOTES

## NEW LIFE MEMBERS

The College is gratified to announce the following additional Life Members, listed in the order of subscription:

Robert S. Dow, M.D., F.A.C.P., Portland, Ore.  
Arthur Lee Osterman, M.D., F.A.C.P., Wheeling, W. Va.  
Everett E. Hammonds, M.D., F.A.C.P., Birmingham, Mich.  
Henry Clay Long, M.D., F.A.C.P., Knoxville, Tenn.  
Delbert H. McNamara, M.D., F.A.C.P., Santa Barbara, Calif.  
Aldis A. Johnson, M.D., F.A.C.P., Council Bluffs, Iowa  
George O. Solem, M.D., F.A.C.P., Chicago, Ill.  
Edward C. Koenig, M.D., F.A.C.P., Buffalo, N. Y.  
James Steele, M.D., F.A.C.P., Brooklyn, N. Y.  
James R. Gudger, M.D., F.A.C.P., New York, N. Y.  
John Noll, Jr., M.D., F.A.C.P., Youngstown, Ohio  
Henry Allen Tadgell, M.D., F.A.C.P., Belchertown, Mass.  
Harry L. Huber, M.D., F.A.C.P., Chicago, Ill.  
George F. Lull, M.D., F.A.C.P., Chicago, Ill.  
Robert Henry Southcombe, M.D., F.A.C.P., Spokane, Wash.

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The Thirteenth Annual Meeting of the American College of Chest Physicians will be held at Atlantic City, N. J., June 5-8. An interesting scientific program has been planned. Oral and written examinations for Fellowship will be held on June 5.

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The American Academy of Allergy and the Medical Faculty of the University of California will offer an Orientation Course in Clinical Allergy for General Practitioners, at the University of California Hospital, San Francisco, July 7-11, 1947. Detailed information concerning this course may be had by writing to Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, Calif.

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The Fourth Annual Meeting of the American Society for Research in Psychosomatic Problems will take place May 3 and 4, 1947, at Haddon Hall, Atlantic City, N. J. Details of program and arrangements may be secured from the Society's office, 714 Madison Ave., New York 21, N. Y.

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The Royal College of Physicians and Surgeons of Canada has announced the following schedule of examinations for the fall of 1947. Applications for these examinations must be in the hands of John E. Plunkett, M.D., F.R.C.P.(C), Honorary Secretary, 150 Metcalfe Street, Ottawa, Can., before June 30.

Written examinations for Fellowship will be held October 27, 28 and 29. Oral and clinical examinations for Fellowship will be held November 24, 25, 26 and 27. Written examinations for Certification will take place October 27 and 28; oral and clinical examinations, November 17 and 18.

Written examinations will be given at Vancouver, Edmonton, Saskatoon, Winnipeg, London, Toronto, Kingstone, Montreal, Quebec City and Halifax. Oral and

clinical examinations will be given at Toronto only. For further information, regulations and application forms, address Dr. Plunkett.

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#### AMERICAN COLLEGE OF PHYSICIANS RESEARCH FELLOWS IN MEDICINE, 1947-48

The Committee on Fellowships and Awards of the College, acting under authorization granted by the Board of Regents, has awarded five additional Research Fellowships in Medicine for the year which begins July 1, 1947. The earlier appointment to a Fellowship for this period of Dr. Tom Fite Paine, Jr., Aberdeen, Miss., was announced last December. Notifications of appointment have been sent to the following physicians.

WARD S. FOWLER, M.D., Philadelphia, Pa. Dr. Fowler will conduct studies of the pathological physiology of certain primary disorders, under the supervision of Dr. Julius H. Comroe, Jr., F.A.C.P., at the Graduate School of Medicine of the University of Pennsylvania. Dr. Fowler is a graduate of Swarthmore College (1937) and of the Harvard Medical School (1941). Dr. Fowler interned at the Philadelphia General Hospital, 1941-42, and served as a medical officer in the U. S. Army Air Forces.

ARNOLD LIVINGSTONE JOHNSON, M.D., C.M., Montreal, Can. Dr. Johnson will continue his investigation of the hemodynamics of congenital heart disease in the Children's Memorial Hospital and the Department of Physiology, McGill University, under the direction of Dr. Alton Goldbloom and Professor H. E. Hoff. Dr. Johnson received the B.A. degree from McGill University in 1935, and his medical degree in 1940. His internship was taken at the Montreal General Hospital in 1941. Dr. Johnson subsequently served as medical officer in the Royal Canadian Navy Medical Corps.

MARY ANN PAYNE, M.D., New York, N. Y. Dr. Payne will undertake at the New York Hospital, where she presently holds appointment as Assistant Resident in Medicine, studies of hepato-renal factors in regard to shock and hypertension. Her supervisors will be Dr. David P. Barr, F.A.C.P., and Dr. Ephraim Shorr. Dr. Payne is a native of Braddock Heights, Md. Her undergraduate work was done at Hood College; she received the degrees of Master of Science (1941) and Doctor of Philosophy (1943) from the University of Wisconsin. Dr. Payne completed her medical course at the Cornell University Medical College in 1945, following which she served as intern in the New York Hospital.

MIRIAM MELLON PENNOYER, M.D., St. Louis, Mo. Dr. Pennoyer, a former resident of Pittsburgh, Pa., received the B.S. degree from Carnegie Institute of Technology in 1935. Her M.D. degree was received from the University of Rochester in 1939. From 1939 to 1944, Dr. Pennoyer engaged in postgraduate work in pediatrics in the University of Minnesota Hospitals.

Dr. Pennoyer will investigate adrenal function in newborn and premature infants at the St. Louis Children's Hospital, under the direction of Professor A. F. Hartmann of the Washington University School of Medicine.

PHILIP FRANKLIN WAGLEY, M.D., Baltimore, Md. Dr. Wagley proposes to study certain mechanisms of hemolysis. These studies will be conducted at the Boston City Hospital, with the supervision of Dr. William B. Castle, F.A.C.P., and Dr. George R. Minot, F.A.C.P.

Dr. Wagley is a native of Mineral Wells, Tex. His undergraduate work was taken at Southern Methodist University, and his medical course at the Johns Hopkins University Medical School, from which he received the M.D. degree in 1943. From 1943 to 1945, Dr. Wagley was intern in pathology and in medicine in the Johns Hopkins Hospital; since 1945 he has held appointment as Instructor in Medicine and Assistant Resident Physician.

President David P. Barr has appointed Walter Freeman, M.D., F.A.C.P., as representative of the American College of Physicians in the Division of Medical Sciences of the National Research Council for a term of three years, beginning July 1, 1947. As College representative, Dr. Freeman will succeed Wallace M. Yater, M.D., F.A.C.P., Governor for the District of Columbia.

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#### REGIONAL MEETINGS OF THE COLLEGE

##### *Richmond, Virginia, February 19*

A very successful Regional Meeting of the College for Fellows and Associates in Virginia was held at the McGuire General Hospital, Richmond, February 19, under the Governorship of Dr. J. Edwin Wood, Jr., Charlottesville.

Dr. Charles M. Caravati, F.A.C.P., Richmond, chairman of the Virginia group, presided at the afternoon session, at which there were about 200 physicians present. The program of this session included some very interesting papers, a number of which were presented by young physicians, some of whom were Associates of The College. The speakers were then brought to the stage together to form a panel of consultants before whom were brought patients illustrating the papers which had been presented.

Speakers following the dinner at the Richmond Academy of Medicine included Dr. Wood; Dr. Edward L. Bortz, Governor for Eastern Pennsylvania; Mr. E. R. Loveland, Executive Secretary of The College; Dr. Walter B. Martin, Regent, Norfolk; Dr. Paul F. Whitaker, Governor for North Carolina, Kinston; Dr. William B. Porter, Richmond, new representative of The College on the American Board of Internal Medicine. Dr. Porter spoke at some length concerning the Board's methods of conducting examinations, and of its plans for improving the written examinations.

##### *Omaha, Nebraska, March 29*

With College Governor Joseph D. McCarthy, M.D., F.A.C.P., as chairman, a Regional Meeting for Nebraska was held at the Omaha Athletic Club on Saturday, March 29. The program of guest speakers at the dinner included Harold C. Lueth, M.D., F.A.C.P., Dean and Professor of Internal Medicine, University of Nebraska College of Medicine, whose topic was "The Internist and the Hospital"; Charles M. Wilhelmj, M.D., Dean and Professor of Physiology, Creighton University School of Medicine, "Neuropsychiatry as a Fundamental in the Treatment of the Internist"; Ralph A. Kinsella, M.D., F.A.C.P., College Governor for Missouri, Professor of Internal Medicine, St. Louis University School of Medicine, who discussed "Trends and Their Effect on Physicians and the Practice of Medicine."

The following scientific papers were presented at the afternoon session: Recent Studies on the Recording of Heart Sounds, by F. Lowell Dunn, M.D., F.A.C.P.; Amebiasis—The Possibility of Missing Correct Diagnosis Because of Related Findings, by Ernest L. MacQuiddy, M.D., F.A.C.P.; Bulbar Poliomyelitis, Epidemiology and Treatment, by J. Harry Murphy, M.D. (Associate); Treatment of Cirrhosis of the Liver, by Ben Slutzky, M.D., F.A.C.P.; Chronic Encephalitis—Irregularities in History: Obscure Physical Findings, by Harrison A. Wigton, M.D., F.A.C.P.; Dermatologic Reactions to Drugs and Antibiotics, by Donald J. Wilson, M.D., F.A.C.P.; all of Omaha; Congestive Heart Failure, by Otto A. Kostal, M.D. (Associate), Hastings; The Choice and Use of Insulin, by Floyd L. Rogers, M.D., F.A.C.P., Lincoln.

*Salt Lake City, Utah, March 29*

With Governor Louis E. Viko, F.A.C.P., as director, a Regional Meeting for the College in Utah was held at Salt Lake City on Saturday, March 29. Fellows and Associates residing in Idaho were also invited to participate. At the time of this writing, the program was not available but will be printed in a later issue.

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The American College of Physicians delivered a check in the amount of \$1,000.00 during January as a donation to the work of The American Heart Association in connection with the Committee on the Study, Prevention and Cure of Rheumatic Fever, a nation-wide project now under way. The title of the Committee has now been officially changed to the American Council on Rheumatic Fever of the American Heart Association, and the member organizations include the American Academy of Pediatrics, American Association of Medical Social Workers, American Heart Association, American Hospital Association, American Medical Association, American Nurses Association, American Public Health Association, American Rheumatism Association, American School Health Association, National Organization for Public Health Nursing, National Society for Crippled Children and Adults and The American College of Physicians.

The Council recently distributed 100,000 copies of its published pamphlet, "Rheumatic Fever, Childhood's Greatest Enemy."

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Arie C. van Ravenswaay, M.D., F.A.C.P., Boonville, Mo., is a recipient of the Legion of Merit. The award was made in recognition of Dr. van Ravenswaay's achievements with respect to preservation of health of personnel of the Army Air Forces during his service in the Army of the United States.

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The Legion of Merit has been conferred upon Dr. William P. Corr, F.A.C.P., Riverside, Calif., who retired from the Army of the United States in January, 1946, with the rank of Colonel. The distinction was won by Dr. Corr's exceptional services as Chief of the Professional Services of Dibble General Hospital, Menlo Park, Calif., October, 1943, to June, 1945. "He displayed at all times a wide knowledge of all phases of internal medicine, quiet yet forceful leadership and high ideals of the practice of medicine."

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The Legion of Merit has been awarded to Colonel John C. Woodland, (MC), USA, Ret'd., F.A.C.P., San Antonio, Tex., for "exceptionally meritorious services" while Chief of Medical Service and Commanding Officer, Brooke General Hospital, December, 1941 to March, 1946. Reference is made to important discoveries which were made concerning virus and rickettsial diseases in studies carried out under Colonel Woodland's supervision.

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Thomas H. Ham, M.D., F.A.C.P., Boston, Mass., who retired from the Army of the United States in May, 1946, with rank of Lieutenant Colonel, is a recipient of the Legion of Merit. The award recognizes Dr. Ham's distinguished accomplishments as a member of the Medical Division, Office of the Chief of Chemical Warfare Service, September, 1943, to January, 1946.

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Dr. Richard H. Lyons, F.A.C.P., Ann Arbor, Mich., Associate Professor of Medicine in the University of Michigan School of Medicine, has been appointed

Edward C. Reifenshtein Professor of Medicine in the Syracuse University School of Medicine. Dr. Lyons will begin his new work in June, 1947.

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Dr. Hugh S. Cumming, F.A.C.P., Washington, D. C., formerly Surgeon General of the U. S. Public Health Service, has been elected Director Emeritus of the Pan American Sanitary Bureau, of which he served as Director for twenty-six years. Dr. Cumming has been succeeded in the latter position by Dr. Fred L. Soper, of the Rockefeller Foundation.

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Dr. Walter A. Bloedorn, F.A.C.P., Washington, D. C., Dean of the George Washington University School of Medicine, has been elected to the position of President-elect of the Society of American Medical Colleges.

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Dr. Albert E. Russell, F.A.C.P., presently attached to the American Consulate General, Naples, Italy, has been promoted to the permanent grade of Medical Director (Colonel) in the U. S. Public Health Service.

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The honorary degree of Doctor of Laws was recently conferred on Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, by Columbia University.

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#### RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to March 13, 1947 inclusive).

Philip K. Arzt, St. Paul, Minn. (Capt., MC, AUS)  
John T. Bennett, Philadelphia, Pa. (Capt., MC, USN)  
William W. Davies, Coral Gables, Fla. (Capt., MC, USN)  
Sidney L. Penner, Stratford, Conn. (Capt., MC, AUS)  
Arthur J. Revell, Pittsburg, Kans. (Lt. Col., MC, AUS)  
David L. Robeson, Kansas City, Mo. (Col., MC, USA)  
Rafael Rodriguez-Molina, Santurce, P. R. (Lt. Col., MC, USA)  
Raymond E. Scott, San Antonio, Tex. (Col., MC, AUS)

## OBITUARIES

## DR. JOHN FAVILL

Dr. John Favill was born in Madison, Wis., September 6, 1886, the son of Henry Baird Favill, distinguished Chicago internist. He died at his home in Winnetka, Ill., December 21, 1946, of coronary thrombosis. He is survived by his widow, Alice Morrell Favill, and a daughter, Elaine, age 10.

Dr. Favill received his A.B. degree from Yale University in 1909; his M.D. degree from Harvard Medical School in 1913. He interned at the Massachusetts General Hospital.

An excellent teacher, Dr. Favill rose to the position of Clinical Professor of Neurology (Rush) in the University of Illinois College of Medicine. He was a diplomate of the American Board of Psychiatry and Neurology. During his career he was affiliated with St. Luke's, Presbyterian, St. Elizabeth's and Cook County Hospitals; also with the Central Free Dispensary and the Institute for Psychoanalysis.

Dr. Favill served as Captain in the Army Expeditionary Force in 1918-19, and as Colonel (inactive status) in the Army Medical Reserve Corps from 1931 on.

He was a Trustee of the Elizabeth McCormick Memorial Foundation. He was a fellow or member of the American Medical Association, American Neurological Association, American Psychiatric Association, Association for Research in Nervous and Mental Diseases, American Society for Psychical Research, Association for the Study of Internal Secretions, Association of Military Surgeons; of the American Birth Control League, National Committee on Planned Parenthood, National Committee for Mental Hygiene, National Dairy Association, American Unitarian Association; of the Institute of Medicine of Chicago and of many state and local medical societies, in a number of which he held offices.

Dr. Favill was the author of more than thirty monographs and papers on medical subjects, and of the following books: "Henry Baird Favill, Life Tribute and Writings," 1917; "Outline of the Cranial Nerves," 1933; "The Relation of Eye Muscles to Semicircular Canal Currents in Rotationally Induced Nystagmus," 1936; "Primer of Celestial Navigation," 1940; "Outline of Spinal Nerves," 1946.

Dr. Favill was scrupulously fair in all of his dealings with others and clung tenaciously to his convictions, regardless of consequences.

GEORGE H. COLEMAN, M.D., F.A.C.P.

## DR. A. LEE BRISKMAN

Dr. A. Lee Briskman was born September 29, 1902, in Louisville, Kentucky, where he lived until 1927 when he took his internship at the

Gorgas Hospital, Canal Zone. Prior to this Dr. Briskman had obtained his B.S. and M.D. degrees from the University of Louisville. Following completion of his internship Dr. Briskman served the Union Printer's Home and Tuberculosis Sanatorium as a resident physician between the dates of 1929 and 1944. During this time he was also instructor in pathology at the Glockner Sanatorium and Hospital.

In 1944 Dr. Briskman moved to Denver as Medical Director of the Jewish Consumptives Relief Society. At the time of his death Dr. Briskman had just resigned from this position with the expectation of entering private practice in Denver.

Dr. Briskman became a Fellow of the American College of Physicians in 1934. He was certified by the American Board of Internal Medicine and was a Fellow of the American Medical Association. He was President of the Colorado Tuberculosis Association. He died suddenly November 26, 1946, while speaking in Colorado Springs in the interests of this organization.

WARD DARLEY, M.D., F.A.C.P.,  
Governor for Colorado

#### DR. JAMES STEWART GAUMER

Dr. James Stewart Gaumer, F.A.C.P., died at Fairfield, Iowa, on September 10, 1946, at the age of 74 years. He was one of the older Fellows of the College, having been elected in 1920.

Dr. Gaumer was born in Victor, Iowa, September 13, 1872, and received his Bachelor of Science degree at Parsons College, after which he entered Rush Medical College in Chicago, graduating with the degree Doctor of Medicine in 1900. He began practice in Danville, Iowa, and moved to Fairfield in 1906, where he continued to practice until the time of his death. His practice was largely limited to internal medicine. He was affiliated with the County and State Medical Societies, and a member of the American Medical Association. For many years he was one of the instructors in the Nurses Training School of Jefferson County Hospital. His military experience began with the Spanish American War when he served as a Sergeant, Company M, 50th Iowa Volunteers; in the World War I he was a Lieutenant in the Medical Corps of the A.U.S.

He is survived by his wife, one son and one grandson.

He was an ethical physician and a high minded citizen.

WALTER L. BIERRING, M.D., F.A.C.P.

#### DR. R. H. M. HARDISTY

The death of Dr. Richard Hardisty in Montreal, Nov. 12, 1946, of coronary thrombosis at the age of 69, brought a great sense of loss to his col-

leagues, friends and patients, as well as to the two institutions which he had served so faithfully and with such distinguished ability, McGill University and the Royal Victoria Hospital.

Graduating from McGill University in Arts and Medicine, Dr. Hardisty served a three year internship at the Royal Victoria Hospital, followed by four years in general practice at Sherbrooke, P. Q., and by a year's post-graduate study in Munich, Berlin, Vienna and London. Dr. Hardisty returned in 1910 to Montreal to practise Internal Medicine with special interest in Gastro-Enterology. He joined the staff of the Medical School in 1930 as Lecturer in Medicine, and the Royal Victoria Hospital as Physician in 1935. He retired to the honorary attending staff in 1943. To both of these institutions he gave untiringly of his outstanding ability as teacher and clinician.

In World War I, Dr. Hardisty served in the Field for over four years with the 6th Canadian Field Ambulance, which he helped to organize, and of which he later became Commanding Officer with the rank of Lt. Colonel. During these years of military service, he was awarded the Distinguished Service Order, the Military Cross, and was twice mentioned in Dispatches, honors which were well merited and worn with all modesty.

He was a member of the Canadian Medical Association, the American Gastro-Enterological Association and Fellow of The American College of Physicians since 1929.

Of his personal side much could be said. Through his unfailing kindness and consideration for others, his rare sense of humor, his unswerving loyalty and his genuineness, he bore the hall mark of the true gentleman and the beloved physician. We in Montreal who knew him well are the poorer for his going, but all the richer for having known him.

He is survived by his widow, the former Elizabeth Porter of Montreal, and by a brother, Alfred.

ARTHUR T. HENDERSON, M.D., F.A.C.P.,  
Governor for Quebec

### DR. LUCIUS NEWTON TODD

Lucius Newton Todd, M.D., F.A.C.P., Augusta, Ga., died after a prolonged illness on December 12, 1946.

Dr. Todd was born in Belton, S. C., October 9, 1890. Following three years of premedical study at Emory University, he attended the University of Georgia School of Medicine and received the M.D. degree in 1915. He interned at the University Hospital, 1915-16. Soon after opening an office in Greenville, S. C., he developed pulmonary tuberculosis. To combat the early rapid progress of this disease required a stamina which few possess and, from 1916 to 1923, Dr. Todd stoically fought an uphill battle at several centers for the treatment of tuberculosis, Saranac Lake, Asheville, and



Colorado Springs. He resumed his medical activities as Resident Physician at Cragmor Sanatorium, 1923-24, and at Sunmount Sanatorium in New Mexico, 1924-25. He served at the U. S. Public Health Service Hospital No. 9 in New Mexico, 1925-28, and was senior resident at the Waverly Hill Sanatorium in Kentucky, 1928-37. In 1937 he was appointed the first Professor of Tuberculosis at the University of Georgia School of Medicine, and Chief of the Tuberculosis Service in the University Hospital. He also acted as Tuberculosis Clinician for the Aiken, S. C., Hospital and Relief Society. Dr. Todd was a Fellow of the American Medical Association; a member of the American Trudeau Society, American College of Chest Physicians; and of the Southern Sanatorium Association (Secretary, 1937-38). He became a Fellow of the American College of Physicians in April, 1944.

As a teacher Dr. Todd possessed the ability to transmit his knowledge and experience to his students. His outstanding success in establishing a Tuberculosis Center was evidenced by his election to honorary membership in the Alpha Omega Alpha Fraternity in 1945. As a physician, his personal experience provided him with a keen understanding of the problems of his patients, and his kindness and encouragement carried the weight of a fellow-sufferer. The Department of Tuberculosis at the University of Georgia School of Medicine will remain as a memorial to its first director and organizer, Dr. Lucius N. Todd.

EDGAR R. PUND, M.D., F.A.C.P.

### DR. ROBERT VAN VALZAH

Robert Van Valzah, M.D., F.A.C.P., was born in Spring Mills, Pa., November 1, 1882. His early education was obtained at Bellefonte Academy, and in 1904 he received an A.B. degree from Princeton University. Upon his graduation from the University of Pennsylvania School of Medicine in 1908, where he was elected to Alpha Omega Alpha, he became the third physician in direct line in his family. This tradition had continued for five generations in this country with but one interruption. In 1908 he served an internship at St. Christopher's Hospital for Children, Philadelphia, after which he became Chief Resident at the Hospital of the University of Pennsylvania in that city.

He joined the Department of Internal Medicine in the University of Wisconsin in 1910, as an instructor, advancing to the position of Professor of Clinical Medicine in 1918. This position he held until his death, November 23, 1946, although, because of ill health, he was granted an official leave of absence in 1935. His position remained open to him with the hope that he would be able to return. In his earlier clinical years he was Director of the Department of Student Health at the University of Wisconsin and later, upon the completion of The State of Wisconsin General

Hospital, he served on its staff. He was a member of the Dane County and the Wisconsin State Medical Societies, and a Diplomate of the American Board of Internal Medicine. During the first World War he was Chairman of the Medical Advisory Board in his district.

To the State of Wisconsin and to the University of Wisconsin Medical School, then in its infancy, Dr. Van Valzah brought an unusual background of medical tradition and training. He was an indefatigable worker, whose life was intimately associated with the student body of the University as physician, and later with the medical students as teacher. His strong character and attractive personality together with a background of excellent medical training did much for the development of the University of Wisconsin Medical School in its pioneering clinical years. At that time he was widely sought as a medical consultant. He was a doctor's doctor, whose memory will be cherished by many people, and whose influence will long be felt by the physicians who trained under him.

KARVER L. PUESTOW, M.D., F.A.C.P.,  
Governor for Wisconsin

### DR. JOSEPH ROSENFELD

Joseph Rosenfeld, M.D., F.A.C.P., Youngstown, Ohio, died November 4, 1946, of periarteritis nodosa, a diagnosis he had long suspected and which was proved at the postmortem examination which he specifically requested be performed on his body.

Dr. Rosenfeld was born in New York City, November 5, 1892, and received the Degree of Doctor of Medicine in 1915 from the Long Island College Hospital. He served as a Medical Officer with the Mount Sinai Unit of New York during World War I, and received honors from the British, French, and American Armies for meritorious service.

He was for many years Associate in Medicine and Instructor of Medicine to Nurses of the Youngstown Hospital. He was a Fellow of the American Medical Association and a member of the Mahoning County Medical Society, Ohio State Medical Association and Cleveland Allergy Society. He became a Fellow of The American College of Physicians in 1940.

Dr. Rosenfeld was a man of many intellectual interests, a fine gentleman, and a credit to his profession.

M. A. BLANKENHORN, M.D., F.A.C.P.,  
Governor for Ohio

### DR. PAUL ROTH

Paul Roth, M.D., F.A.C.P., of Battle Creek, Michigan, died November 6, 1946. He was born in Tramelan, Switzerland, July 9, 1871; he received his early elementary education in that country. He attended the Battle

Creek College and received his medical degree from the American Medical Missionary College (Chicago) in 1904. He interned at the Battle Creek Sanitarium and served there in numerous capacities after 1910. He was at one time on the faculty of the Battle Creek College, and Consultant in Oxygen and Carbon Dioxide Therapy at the Kellogg Foundation.

He was a member of the Calhoun County Medical Society, Michigan State Medical Society, American Medical Association, Association for the Study of Endocrinology, the American Chemical Society. He became a Fellow of the College in 1920.

DOUGLAS DONALD, M.D., F.A.C.P.,  
Governor for Michigan

### DR. ROBERT IVAN BAXMEIER

Robert Ivan Baxmeier, M.D., F.A.C.P., of Pittsburgh, Pa., died June 27, 1946, of coronary thrombosis. Dr. Baxmeier was born in Pittsburgh, July 31, 1904. He received the degree of Bachelor of Science in 1926 at the University of Pittsburgh and the degree of Doctor of Medicine in 1930 from the Hahnemann Medical College of Philadelphia.

Following his internship in the Shadyside Hospital, Pittsburgh, Dr. Baxmeier continued his medical studies at the University of Chicago and in a number of courses presented by the American College of Physicians. He engaged in practice in Pittsburgh, devoting himself largely to Internal Medicine and Gastro-enterology. He became the Head of the Department of Gastro-enterology in the Shadyside Hospital.

Dr. Baxmeier was a member of the Allegheny County Medical Society of the State of Pennsylvania, Homeopathic Medical Society of the State of Pennsylvania, American Heart Association, and American Gastroscopic Club; he was also a Fellow of the American Medical Association, and became a Fellow of the American College of Physicians in 1944.

### DR. TRIMBLE JOHNSON

Trimble Johnson, M.D., F.A.C.P., was born at Atlanta, Ga., on December 3, 1894. His elementary education was obtained in Atlanta schools and at the Staunton Military Academy. He took a pre-medical course at the Georgia School of Technology and his medical course at Emory University, from which he obtained the Doctor of Medicine degree in 1918. He served as intern at the Grady Memorial Hospital, Atlanta, and the Charity Hospital, New Orleans.

Dr. Johnson specialized in Internal Medicine and Gastro-enterology. He held appointments as Visiting Physician to the Grady Memorial Hospital and to the Anti-Tuberculosis Association Clinic and Good Samaritan Clinic, as well as to the Crawford W. Long Memorial Hospital.

Dr. Johnson became a Fellow of the American College of Physicians in 1929.

Dr. Johnson's death, attributable to pulmonary tuberculosis, occurred October 6, 1946.

### DR. ISIDORE WILLIAM HELD

Dr. Isidore William Held, New York City, died at the Mount Sinai Hospital on Sunday, March 2, 1947, at the age of seventy.

Dr. Held was born in Boryslav, Austria, May 15, 1876. He received his medical degree from the Jefferson Medical College of Philadelphia in 1902, and took postgraduate work in Berlin and Vienna. Dr. Held was active in the practice of medicine in the vicinity of New York City. He was Consulting Physician at the Nathan and Miriam Barnert Memorial Hospital, Paterson, N. J.; at the Israel-Zion, Beth-El and Beth Moses Hospitals, Brooklyn; Jewish Memorial and Beth Israel Hospitals, Manhattan; and the Rockaway Beach Hospital, Queens. Dr. Held became Clinical Professor of Medicine in the New York University in 1935, a position which he held until 1941. In 1945 a Fellowship fund was contributed by a group of his friends to the University in his honor.

Dr. Held was the author of 86 monographs and articles on gastroenterology, hematology, roentgenology, cardiology and medical biography. In 1946, his medical work, "Peptic Ulcer," written in conjunction with Dr. A. Allen Goldbloom, was published.

Dr. Held was a Diplomate of the American Board of Internal Medicine; and a Fellow of the American College of Physicians since 1931, New York Academy of Medicine, American Medical Association and National Gastroenterological Association. He was a member of the American Heart Association, American Association for the Advancement of Science, Association of Military Surgeons, American-Soviet Medical Society and the State and County Medical Societies.

A Founder of the Federation for the Support of Jewish Philanthropic Societies of New York, Dr. Held was a member of the National Council of the American Jewish Joint Distribution Committee, and a founder of the American Jewish Physicians Committee.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

### DR. JOHN T. O'MARA

The College has just received information of the death, March 3, 1946, of John T. O'Mara, M.D., F.A.C.P. of Baltimore, Md.

Dr. O'Mara was born at Baltimore County, Md., in 1880. He attended Mount St. Joseph College and received his medical education at the Uni-

versity of Maryland School of Medicine and College of Physicians and Surgeons, graduating in 1903.

Dr. O'Mara served for many years on the Medical Staff of St. Agnes' Hospital and was at one time Chief of Staff.

Dr. O'Mara became a Fellow of The American College of Physicians in 1921. He was also a Fellow of the American Medical Association, and a member of the Baltimore City Medical Society, Medical and Chirurgical Faculty of Maryland, and the Southern Medical Association.

### DR. MIGUEL ROSES-ARTAU

Miguel Roses-Artau, M.D., F.A.C.P., of San Juan, P. R., died in his residence on July 17, 1945, at the age of 71. At the time of his death he was still in active practice as Chief Radiologist to the Arecibo District Charity Hospital and the San Juan District Penitentiary.

Dr. Roses-Artau was born on August 9, 1874, in Palma de Mallorca, Spain. He came to Puerto Rico in his childhood and received his college and medical education at Maryland Medical College, graduating in 1904. For several years he worked in Arecibo, P. R. In 1912 he returned to Spain, where he pursued postgraduate work at the Pharmaceutical Institute of Barcelona. Upon his return to the island, he renewed his practice in the city of Arecibo, and later moved to San Juan.

During his first years in practice, Dr. Roses-Artau had the privilege of being one of the collaborators of Dr. Ashford in his work on schistosomiasis. Dr. Roses-Artau later devoted most of his time to the specialty of radiology, in which he performed a most conscientious job. He was appointed a member of the Insular Board of Health in 1926.

Dr. Roses-Artau became a Fellow of The American College of Physicians in 1926.

RAMON M. SUAREZ, M.D., F.A.C.P.,  
Governor for Puerto Rico

### DR. GEORGE ANDREW CHAPMAN

George Andrew Chapman, M.D., F.A.C.P., died December 16, 1946 at Glens Falls, N. Y., from uremia.

Dr. Chapman was born at Glens Falls in 1871. He received his medical education at the Baltimore Medical College, from which he obtained his degree in 1897. He undertook postgraduate studies at the University of Maryland Medical School in 1913.

Dr. Chapman was a veteran of the Spanish-American War. For many years he was the Health Officer of Queensbury. For many years also, he was affiliated, as Attending Physician, with the Glens Falls Hospital.

Dr. Chapman was a member of the American Public Health Association, American Association for the Advancement of Science, and the New York

State Society of Internal Medicine. He was a past President of the Medical Society of the State of New York and of the Warren County Medical Society. Dr. Chapman became a Fellow of the American College of Physicians in 1925.

Dr. Chapman's death at the age of 75 caused a distinct loss to the community in which he served.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,  
Governor for Western New York

### DR. HAROLD PHILLIPS HILL

Harold Phillips Hill, M.D., F.A.C.P., San Francisco, Calif., died December 3, 1946. His death marked the loss of another of the older and traditionally great internists of California. He was born in Waterbury, Vt., on August 5, 1877. His father, also a physician, practiced in Redlands, Calif., for over 40 years.

In 1898 Dr. Hill graduated with distinction from Stanford University, going from there to the University of California, where he received his M.D. degree in 1901.

From 1901 to 1902 he interned at St. Luke's Hospital in San Francisco, and was associated in practice in San Francisco with Dr. Clark J. Burnham from 1902 to 1908, when the latter moved to Berkeley.

Dr. Hill was Chief of the Medical Service at St. Luke's Hospital from 1905 to 1946. In 1913 he left the University of California, where he had served as Instructor in Physiology and Assistant Professor of Medicine, to become Clinical Professor of Medicine at the Stanford University School of Medicine. He was also appointed as Chief of Medicine on the Stanford Medical School Service at the San Francisco Hospital, where he held regular medical rounds and taught groups of students. His teaching was characterized by a very practical approach, and his painstaking and thorough examination of patients made a lasting impression on his students.

Dr. Hill's society memberships included the San Francisco County and California State Medical Societies; the American Medical Association; San Francisco Academy of Medicine. He became a Fellow of the American College of Physicians in 1932. In addition he was a member of the Phi Delta Theta, Nu Sigma Nu, Sigma Xi and Alpha Omega Alpha societies. He was a Diplomate of the American Board of Internal Medicine and a preceptor with the Board for several years.

As a consultant and teacher, Dr. Hill wielded a great influence in this community; his intense devotion to his patients and to the responsibilities of an outstanding teacher and internist remains as an example and inspiration to those of us who carry on in his stead.

ERNEST H. FALCONER, M.D., F.A.C.P.,  
Governor for Northern California

## DR. THOMAS HALL SHASTID

Dr. Thomas Hall Shastid, F.A.C.P., died of uremia, February 15, 1947, at Duluth, Minnesota. He was born in Pittsfield, Illinois on July 19, 1866. Dr. Shastid was a student at Eureka (Ill.) College, 1883-1886, at the Medical Department of Columbia University 1886-1887 and at the University of Vermont College of Medicine, from which he graduated with an M.D. degree in 1888. He pursued a course of postgraduate study at the University of Vienna, 1888-1889, and received an A.B. degree cum laude from Harvard University in 1893. Dr. Shastid received A.M. and LL.B. degrees from the University of Michigan in 1901 and 1902 respectively. He was certified by the American Board of Ophthalmology in 1917 and received the honorary degree of Sc.D. from the University of Wisconsin in 1922. He began practice of medicine in Pittsfield, Illinois in 1889 and held the chair of Professor of the History of Medicine at the American Medical College of St. Louis from 1907 to 1912. In 1922 Dr. Shastid moved to Duluth, Minnesota where he became Consulting Ophthalmologist to St. Mary's and Miller Memorial Hospitals in Duluth, and St. Mary's Hospital in Superior, Wisconsin. He was also Visiting Ophthalmologist to St. Luke's Hospital, Duluth, Minnesota. He was a fellow of the A. M. A., American Academy of Medicine, American Medico-Legal and Toxicological Society, American Academy of Ophthalmology and Oto-Laryngology, American College of Surgeons, American College of Physicians and member of the American Association for Advancement of Science, National Society for Prevention of Blindness, American Association of the History of Medicine, International Congress of Ophthalmology, Author's League of America, Eugene Field Society, Société Académique d'Histoire Internationale, Arts et Belles-Lettres and other societies. Dr. Shastid was the author of numerous scientific articles and several novels. He was the inventor of several instruments for the study and treatment of diseases of the eyes, ears, nose and throat and was a public lecturer on animals' eyes, light, blindness, permanent international peace and other subjects.

E. V. ALLEN, M.D., F.A.C.P.,  
Governor for Minnesota

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## THE USE OF FOLIC ACID IN SPRUE \*

By RAMÓN M. SUÁREZ, M.D., F.A.C.P., *Santurce, San Juan, P. R.*, TOM  
D. SPIES, M.D., F.A.C.P., and RAMÓN M. SUÁREZ, JR., M.D.

A NUMBER of investigators have already shown that Addisonian pernicious anemia, non-tropical sprue, and related macrocytic anemias are promptly relieved by the administration of synthetic folic acid (*Lactobacillus casei* factor).<sup>1, 2, 3, 4, 5, 6, 7, 8</sup> Spies and his collaborators from Cincinnati, Birmingham, Cuba and Puerto Rico<sup>9, 10, 11</sup> have reported a remarkable effect on persons suffering from tropical sprue. The discovery of the effect of this drug on certain types of macrocytic anemia in relapse opens up a new era in the study of anemia.

The University of Cincinnati and the School of Tropical Medicine at San Juan, Puerto Rico commenced a coöperative study of the treatment of tropical sprue with folic acid in November 1945. Some of the cases studied have now been followed for more than four months. The clinical and hematological responses of these patients have been so impressive that it seems worthwhile to report some of our observations.

This report is based on the study of 50 cases of sprue. Twenty-two were acute, full-blown cases of the disease. The rest were old cases that had been maintained in relatively good health for a number of months, or years, under adequate liver therapy. The former were treated from the start with folic acid, while the others were transferred from parenteral liver therapy to the oral administration of folic acid.

The effectiveness of folic acid in the treatment of sprue having been established, we have endeavored to determine:

\* Presented at the Twenty-Seventh Annual Session of the American College of Physicians, Philadelphia, May 17, 1946.

From the School of Tropical Medicine of Puerto Rico and from the University of Cincinnati.

In the medical care of the patients we were assisted by Dr. Caroline K. Pratt, Dr. Dwight Santiago-Stevenson and Dr. Federico Hernandez-Morales. The determination of the fat was done by Dr. C. F. Asenjo, the chemical studies by Dr. R. Ruiz Nazario, and the study of the reticulocytes and bone marrow by Miss Clemencia Benitez-Gautier.

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1. Optimum oral dose.
2. Effect of this dose in the presence of an inadequate diet low in meat, meat products, fish and eggs, from which liver and yeast have been excluded.
3. Effect in the presence of an adequate diet, high in animal proteins, and low in fats and carbohydrates.
4. Effect upon the glucose tolerance curve and upon the fat content of the stools.
5. Maintenance dose of folic acid.
6. Whether folic acid can be substituted for parenteral liver extract in the treatment of old chronic cases of sprue.

Since the pathogenesis of the macrocytic anemias is not thoroughly understood and there is much confusion concerning their diagnosis, we were very careful in the selection of our cases. A clinical diagnosis of sprue is possible in the tropics, but it cannot be established on firm grounds without the help of the laboratory. A combination of glossitis, anemia, loss of weight and diarrhea, with or without steatorrhea, may be observed in various conditions unrelated to sprue. We have seen cases of simple achlorhydric anemia, hookworm anemia, syphilitic glossitis, intestinal and peritoneal tuberculosis, Hodgkin's disease of the mesenteric glands, certain anemias associated with pregnancy, chronic enteritis and colitis, neoplastic diseases and cases of Addisonian pernicious anemia diagnosed and treated as sprue. On the other hand, in our own series, we have proved cases of sprue in which the intense pigmentation and low blood pressure strongly suggested Addison's disease.

We based our selection of cases on the following criteria: the patient is usually a white, young or middle-aged individual (age may range from 9 to 84 years), who complains of general weakness, diarrhea, and glossitis persisting off and on for months or years. On physical examination, there is evident loss of weight with signs of premature aging, some abdominal distention, and pronounced anemia. Careful inspection often reveals that the skin and conjunctivae do not present the same pallor observed in hookworm disease and other iron-deficiency anemias, but rather a yellowish or mild sub-icteric tint.

The patient may complain of cramps in the legs, but rarely (2 per cent) will show neurological signs and symptoms of combined system disease. Unless liver therapy has been given previously, the patient will show a macrocytic hyperchromic type of anemia and a megaloblastic bone marrow indistinguishable from that of pernicious anemia. In our experience, this is the most constant laboratory finding. There is often steatorrhea with predominance of fatty acids and soaps, and a flat glucose tolerance curve. Gastric analysis will show either hypochlorhydria or histamine-resistant achlorhydria (20 to 30 per cent). In 70 per cent of the cases, roentgen investigation of the small intestine reveals the so-called "deficiency pattern," or "moulage" sign (figure 1).

The 22 patients who had full-blown sprue were all white, of ages ranging between 18 and 67; 17 were males and five females. Twenty were hospitalized at the University Hospital and two at Mimiya Hospital.

Seventeen of the 22 patients with acute sprue were kept from three to eight weeks on what we call a "preliminary" sprue diet, which is supposed to be similar to that which our ward patients receive at home. This diet con-

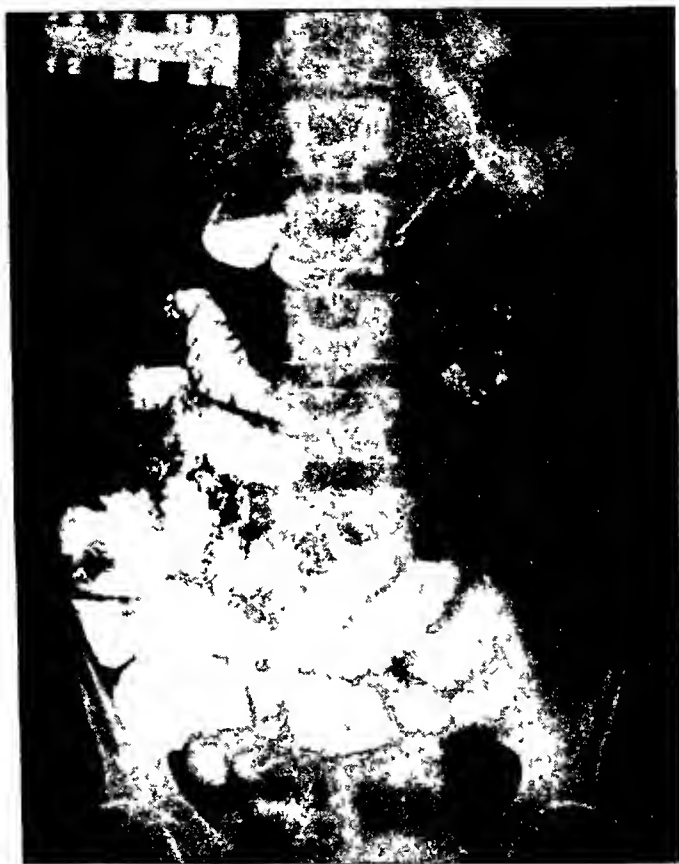


FIG. 1. Typical "moulage" sign in sprue.

sists almost entirely of polished rice, kidney beans and root vegetables, with very little milk, a weekly allowance of not over one half pound of meat and one egg. Occasionally a little codfish is added, but no poultry, cheese, liver or yeast. Four of these patients received 50 mg. of folic acid daily "per os" for about two weeks; after this the dose was reduced to 20 mg. daily. Three patients were given only 5 mg. daily for 10 to 14 days. Subsequently, large single doses of 100 and 500 mg. were tried on these three. In eight cases, the initial dose of folic acid was 20 mg. daily. One patient was given a single dose of 200 mg. and its effect observed for 18 days, when 20 mg. daily were administered. The last of the 17 patients received 100 mg. daily for 10 days, at the end of which the dose was also reduced to 20 mg. daily.

During the course of treatment, and after a period of observation lasting from three to eight weeks, the diet of the 17 patients was changed to "full" sprue diet, rich in animal proteins and vitamins, low in fats and carbohydrates. The remaining five patients studied were given the "full" sprue diet from the beginning of treatment and the effect of 10, 20, and 50 mg. daily doses of folic acid was observed.

TABLE I  
Sprue  
(New Cases)  
Initial Blood Picture

Case	Unit Number	RBC (Mill.)	Hgb. (Gm.)	WBC (Thous.)	M.C.V. (Cu. Mic.)	Reticu- lyocytes	Platelets
1	A 7795	.6	2.4	1.5	130	0	80
2	A 7816	1.0	4.9	2.6	160	0	90
3	A 6815	1.7	8.4	3.1	143	.2	140
4	A 7647	2.3	10.1	6.2	135	0	100
5	A 7855	1.7	8.7	7.3	134	.2	150
6	A 7885	1.6	6.6	1.7	114	0	124
7	A 7868	2.0	6.0	4.3	113	0	140
8	A 7910	3.0	12.7	4.9	133	.1	94
9	A 7946	1.3	4.9	1.9	118	.4	100
10	A 7939	1.3	4.9	4.8	123	.4	106
11	A 8011	3.0	11.6	4.2	112	0	80
12	A 8049	.9	4.0	2.6	107	0	
13	A 8099	1.8	7.8	3.2	125	15.8	86
14	A 8079	1.5	7.4	3.3	160	5.2	
15	A 8054	2.4	11.1	5.3	143	3.2	
16	A 8128	.9	3.6	1.4	129	0	90
17	A 7956	2.4	10.2	2.8	133	4	118
18	A 8114	1.8	8.4	3.0	159	3.2	72
19	J.D.	2.1	9.9	3.2	126	.2	204
20	A.L.	1.7	7.7	2.8	165	0	216
21	A 8206	2.4	10.5	2.0	133	2	112
22	A 8291	2.2	10.5	5.8	135		
Average		1.7	7.8	3.5	133.1	.14	116.7

In case 1, the patient was so severely ill on admission that we did not deem it safe to postpone treatment. In all the other cases, folic acid was withheld until laboratory examinations had been performed and baseline determinations established. This ordinarily took about a week.

*Peripheral Blood.* Daily hematocrit studies, using heparinized venous blood, were carried out for the first 10 or 14 days, and at weekly intervals thereafter. All pipettes used for the blood counts were certified by the U. S. Bureau of Standards. The hemoglobin content was determined in grams and per cent by means of the Photovolt photoelectric hemoglobino-meter, calibrated so that 14.5 grams was equivalent to 100 per cent. The reticulocytes were counted in dry preparations of brilliant cresyl blue, counterstained with Wright's stain. Platelets were enumerated in the counting chamber used for red blood cells, by means of a fresh solution of sodium citrate.

Table 1 shows the peripheral blood picture in 22 cases of sprue on ad-

mission to the hospital. It should be stated that when folic acid was started, about one week later, the figures for red blood cells and hemoglobin were usually lower. Two patients (numbers 13 and 14) had a spontaneous reticulocytosis of 15.8 and 5.2 per cent, respectively, from one to three days after entry, but this rapidly disappeared. When treatment was instituted, none of the patients had more than 2 per cent of reticulocytes, the usual count being 0 or 0.2 per cent. The erythrocyte counts ranged from 600,000 to 3,000,000 per cubic millimeter; the hemoglobin from 2.4 to 11.6 grams per 100 c.c. Red blood cell counts were below 2,500,000 per cubic millimeter in all cases but two. The leukocytes ranged from 1,500 to 7,300 per cubic millimeter. In nine cases the leukocyte count was less than 3,000 per cubic millimeter. The mean cell volume varied from 107 to 165 cubic microns, with an average of 133.1 cubic microns, and the platelets from 80,000 to 216,000 per cubic millimeter, with an average of 116,700 per cubic millimeter. In every case, therefore, macrocytic anemia was present.

*The Sternal Marrow.* In all cases, the sternal bone marrow was obtained by aspiration, prior to treatment, and again three to five days and one month later. Differential counts of 500 nucleated cells were made, by means of Jenner-Giemsa or Wright stain, decolorized with a solution of 0.5 c.c. acetone, 5.0 c.c. methyl alcohol, and freshly distilled water, pH 6 to 6.4–100.0 c.c. We found the latter procedure quite satisfactory

TABLE II  
Sternal Marrow  
(Initial Counts)

Case	Megalo- blasts	Erythro- blasts— early	Erythro- blasts— late	Normo- blasts	Granulo- cytic series	Lympho- cytic series	Plasma cells	Megakaryo- cytes
1	5.6	6.6	9.8	18.6	47.6	10.6	1.2	0
2	12.2	11.2	11.0	15.6	38.4	10.2	1.4	0
3	2.2	5.6	9.2	18.0	42.0	22.0	.6	0
4	3.0	3.4	11.8	13.6	51.4	16.2	.2	0
5	7.8	6.6	7.2	11.8	57.8	8.4	.2	0
6	12.0	14.2	9.6	6.6	42.0	14.6	1.0	0
7	7.8	7.2	9.6	9.8	60.0	4.6	.8	0
8	.5	3.5	12.0	19.5	58.0	2.5	3.0	.5
9	31.0	22.4	13.0	5.2	25.6	1.6	1.0	0
10	14.6	12.4	11.0	4.4	48.0	8.2	1.2	0
11	9.8	10.6	8.6	4.8	51.8	11.6	2.2	.6
12	22.0	12.8	12.6	2.4	42.4	7.4	.4	0
13	25.6	18.4	12.8	4.0	32.2	4.8	1.2	.6
14	25.8	11.2	8.4	9.4	34.2	10.0	1.0	0
15	7.4	9.2	9.8	8.0	60.2	4.4	.6	.2
16	25.2	23.8	11.2	3.2	29.6	5.4	1.4	0
17	1.8	5.0	5.2	4.8	74.6	7.2	1.0	0
18	19.4	13.8	10.0	10.8	41.8	3.4	.4	.2
19	20.2	16.0	9.2	11.8	39.0	3.2	.6	0
20	27.0	19.4	16.0	8.2	23.6	5.0	.6	.2
21	13.8	10.8	9.6	16.0	39.4	7.0	2.6	.6
22	8.2	5.8	6.0	11.4	48.0	19.0	1.2	.2
Ave.	12.9	11.1	9.9	9.4	42.9	7.7	1.0	.1

Table 2 shows the differential counts of the aspirated sternal marrow of the 22 patients prior to treatment. The lowest megaloblast count was 0.5 per cent in case 8, and the highest 31 per cent in case 9. The average megaloblast count was 12.9 per cent. Early erythroblasts ranged between 3.4 and 23.8 per cent, with an average of 11.1 per cent. Normoblasts ranged between 2.4 and 19.5 per cent, with an average of 9.4. The granulocytic elements ranged between 23.6 and 74.6 per cent, with an average of 42.9. Cells of the lymphocytic series ranged from 1.6 to 22 per cent, with an average of 7.7. Plasma cells ranged from 0 to 3 per cent, and megakaryocytes from 0 to 0.6 per cent. All cases but one showed the typical erythroblastic arrest observed in pernicious anemia.

TABLE III  
Blood Chemistry

Case	N.P.N.	Urea N	Sugar	Cholesterol	Phosphorus	Phosphatase B. units	I.I.	Calcium
2	28.1	12.8	103.0	145.6	3.3			9.2
3	23.3	9.6	92.6	112.0	3.6	2.5		10.0
4	30.3	12.7	88.5	149.2	4.2	2.6		10.8
5	22.8	12.6	101.0	110.8	2.1	3.0	3.19	9.0
6	26.7	12.0	101.0	131.0	4.3	2.0		8.2
7	23.7	8.1	88.9	162.2	4.9	3.4	5.83	9.6
10	23.0	9.7	97.1	109.8	3.9	2.2	10.00	9.6
11	27.2	9.9	88.5	136.4				7.2
12	22.0	8.4	101.0	144.2	3.7	2.6	8.60	9.6
13	38.1	14.1	98.5	167.6	3.6	4.2		10.2
14	29.2	9.1	98.5	141.6	3.2	3.9	9.00	10.0
15	33.8	8.2	90.1	131.6	3.3	3.3		8.8
16	24.6	13.5	101.0	186.0	3.6	2.1	9.80	8.0
17	29.0	9.3	93.0	139.8	3.8	5.2		12.8
18	26.1	9.2	106.0	176.0	3.0	3.1		11.2
19	28.3	8.1	106.0	151.0	3.3	3.8		9.0
Ave.	27.2	10.4	97.1	143.4	3.5	3.1	7.7	9.5

*Blood Chemistry.* Table 3 shows that non-protein nitrogen, urea nitrogen, sugar, and phosphorus concentrations were normal in all patients tested. If we accept 150 to 230 mg. per cent as the normal for total blood cholesterol, our series of cases show either a low or a normal blood cholesterol. Hypercholesteremia was not encountered. The range was 109.8 to 186 mg. per cent. Eleven of the 16 cases examined showed low total cholesterol. Cholesterol esters were not determined. Phosphatase ranged from 2 to 5.2 Bodansky units (two cases were above normal), the icterus index from 3.19 to 10 units (all but two were above 6), and serum calcium from 7.2 to 12.8 mg. per cent, with an average of 9.5 mg. per cent. (Four of the 16 patients tested showed values below 9 mg. per cent.)

These figures agree with those obtained by us in a larger series (70 cases) studied at the University Hospital, the data of which have not yet

been published. In that series, the total blood cholesterol ranged from 60 to 190 mg. per hundred c.c., with an average of 127 mg.; phosphatase from 1 to 11 units, with an average of 3.5 units; serum calcium from 6 to 11 mg. per cent, with an average of 8.1 mg.; glucose, non-protein nitrogen, urea nitrogen, inorganic phosphorus, uric acid, creatinine and chlorides all being normal.

TABLE IV  
Blood Proteins  
(Gm.  $\times$  100)

Case	Total	Albumin	Globulin
1	5.88	4.55	1.33
2	5.76	3.34	2.42
3	6.98	3.90	3.09
4	5.71	3.84	1.87
5	6.0	3.7	2.3
6	6.0	4.1	1.9
7	5.67	3.67	2.0
10	8.79	5.56	3.23
11	4.00	3.00	1.00
12	6.69	4.92	1.77
13	6.93	4.47	2.46
14	8.93	5.29	3.64
15	6.82	3.61	3.21
16	5.28	3.55	1.73
17	7.79	3.58	4.21
18	6.73	4.25	2.48
19	6.57	4.01	2.46
Ave.	6.5	4.7	2.4

*Blood Proteins.* The total blood proteins, as determined in 17 cases (table 4), ranged between 4.00 to 8.93 per 100 c.c. of serum, with an average of 6.5 gm. per cent; the albumin component from 3.00 to 5.29 per cent, with an average of 4.7 gm. per cent; and the globulin from 1 to 4.21 gm. per cent, with an average of 2.4 gm. per cent. In six cases there was moderate hypoproteinemia and in six of the 17 cases an alteration of the albumin-globulin ratio was observed.

These figures again agreed with those in our larger series of 70 patients, who gave the following findings: total serum proteins from 4.5 to 9.5 gm. per cent, with an average of 7.2; serum albumin from 1.5 to 6 gm., with an average of 3.8 gm. per cent, and serum globulin from 1.5 to 5 gm. with an average of 3.1 gm. per cent.

*Gastric Analysis.* The gastric secretion in sprue shows hypochlorhydria in about 70 per cent of cases and histamine-resistant achlorhydria in about 30 per cent. Hyperchlorhydria is rare. In a series of 150 cases reported by us<sup>12</sup> only one showed hyperchlorhydria. There was not a single instance of hyperchlorhydria in 100 cases of sprue reported by Rodriguez Molina<sup>13</sup> and in 100 cases recently studied at the University Hospital, only 14 per cent had a free HCl above 80° following histamine stimulation.

TABLE V  
Gastric Analysis  
Free HCl

Case	Fasting	Histamine			
		1st	2nd	3rd	4th
2	0	0	8°	10°	0
3	0	0	8°	10°	0
4	0	42°	36°	50°	52°
5	0	30°	86°	42°	0
6	0	0	0	0	0
7	0	16°	82°	56°	36°
8	0	0	0	10°	0
9	0	10°	12°	0	0
10	0	0	20°	16°	28°
11	0	0	0	0	0
12	0	0	0	18°	10°
13	0	0	32°	22°	56°
14	0	0	0	0	0
15	0	0	0	0	0
17	0	0	51°	48°	14°
18	0	44°	28°	14°	12°
20	0	0	0	0	16°
21	10°	12°	46°	52°	58°

Table 5 shows the results obtained in the fractional analysis of gastric secretion, limited to free HCl, using histamine stimulation in the present group of cases. It will be seen that there was no free HCl in the fasting contents of the stomach in 21 cases. One had 10°. Some free HCl appeared following histamine administration in all but four. The four cases showing histamine resistant achlorhydria were cases number 6, 11, 14 and 15 of 25, 36, 58 and 56 years, respectively. Only two cases in the group showed a free HCl in excess of 80°.

*The Stools.* The stools in sprue have been described as white, copious, liquid, foamy, fermenting, and foul smelling. From three to 20 bowel movements a day is the usual number. A normal individual excretes about 200 gm. of feces daily, whereas the sprue patient passes from 400 to 1200 gm. Not all sprue patients have white stools; most of them pass gray stools, and in a number of cases the stools are green or dark colored, but usually acid and abundant.

*Urobilinogen.* The pallor of the sprue stool is not due to lack of bile, for this is present in normal amounts. It has been stated\* that "bile is present in a colorless state urobilinogen." Our studies of urobilinogen content of the stools and urine in 13 cases of the present series and in 59 additional cases show that with only one exception, the urobilinogen content of the stools was found in normal amounts, or more often below the normal minimum. In the present series (table 6), the range was from 0.8 to 148.8 mg. with an average of 26 mg. (The normal, according to Watson's method, varies from 40 to

\* Manson Bahr, Philip H.: *Manson's Tropical Diseases*, 1940, The Williams & Wilkins Co., Baltimore, Md.

240 mg. in 24 hours.) The urobilinogen in the urine was normal; from 0 to 0.15 mg. elimination in 24 hours.

TABLE VI  
Urobilinogen  
Watson's Method  
(Mg. in 24 hrs.)

Case	Stools	Urine
1	10.1	0
2	5.4	
3	41.2	0
5	20.4	0
6	148.8	.15
7	49.4	
8	4.9	0
9	.8	0
10	9.9	.03
11	3.2	0
12	7.6	0
13	11.0	0
Ave.	26.0	

The fecal fats were studied by Dr. C. F. Asensjo, of our Department of Chemistry, in 19 cases of active sprue, some before and some after the administration of folic acid, and in five old sprue cases which were at the time apparently controlled. The average figures of the analyses of 13 samples of stool from four normal subjects serve as standard for comparison.

TABLE VII  
Fat Content of the Stool  
(Method of Kayne, Lebner and Connor)  
Active Sprue Before Treatment

Initials	% Solid in fresh feces	% Total fats in dried feces	Partition of fats—% Total fats				
			Split fats			Neutral fats	Unsap.
			Free acids	Soaps	Total		
J. R.	21.34	24.09	85.59	6.39	92.48	5.33	2.19
E. H.	19.34	29.49	83.59	2.65	86.24	9.73	4.03
A. H.	31.80	24.99	80.58	2.90	83.48		
M. S.	8.79	62.06	88.92	1.89	90.81	16.52	
M. V.	10.26	22.06	80.33	7.44	87.77	9.19	
N. R.	2.51	17.59	87.10	4.15	91.25	12.23	
J. D.	5.79	23.35	77.60	8.20	85.80	8.76	
N. S.	7.61	8.56	69.86	8.22	78.08	14.19	
F. N.	4.40	18.59	64.06	6.91	70.97	16.99	4.99
R. D.	20.90	50.99	81.95	4.91	86.05	16.36	1.27
C. O.	18.30	13.07	73.72	11.54	85.76	17.95	
F. C.	6.40	22.73	78.42	5.55	83.97	11.27	3.45
						11.84	4.19
Ave.	19.18	26.46	79.31	6.48	85.22		



Table 7 shows the fat content of the stools in 12 cases of acute sprue before the administration of folic acid. The percentage of total fats in the dried feces ranged from 8.56 to 62.06 with an average of 26.46, the free fatty acids ranged from 64.06 to 88.92, with an average of 79.31, soaps from 1.89 to 11.54 with an average of 6.48, and the total split fats from 70.97 to 92.48 with an average of 85.22. It will be seen that in only two instances was the percentage of total fats in dried feces above 30, but that total split fats were above 77 per cent in all cases but one.

TABLE VIII  
Fat Content of the Stools  
(Method of Kayne, Lebner and Connor)  
During Folic Acid Administration

Initials	% Solid in fresh feces	% Total fats in dried feces	Partition of fats—% Total fats				
			Split fats			Neutral fats	Unsap.
			Free acids	Soaps	Total		
E. V.	12.30	39.82	78.11	3.57	81.67	15.33	2.97
E. P.	23.30	26.28	85.45	2.57	88.02	9.73	2.25
M. S.	10.55	18.82	45.52	4.94	50.46	39.35	1.02
E. F.	4.27	19.01	50.23	7.04	57.27	41.08	1.64
R. B.	19.99	15.71	69.91	4.05	73.96	26.04	1.56
C. O.	23.60	17.77	81.51	5.32	86.93	11.61	
J. M.	11.14	14.76	72.80	3.78	76.48	18.38	5.18
M. G.	9.38	13.92	55.13	11.91	67.04	27.50	5.45
Ave.	13.19	20.76	67.33	5.40	72.75		

Determinations performed on eight cases a few days following the administration of folic acid (table 8) showed that although the stools were still liquid or soft as evidenced by a low percentage of solids (13.19 per cent), the amount of total fats in the dried feces had diminished to 20.76 per cent; the free fatty acids to 67.33 per cent, and the total split fats to 72.75 per cent.

In table 9 appears a comparison of the fat content of the stools in cases of untreated active sprue, cases of active sprue under folic acid therapy for a few days, cases of sprue apparently arrested under parenteral liver therapy administered for many months or years, and the average for four normal subjects in Puerto Rico.

Parasitological examination of the stools in this series of 22 patients showed that one half of them harbored *Necator americanus* in the intestine, two had eggs of *Schistosoma mansoni*, seven *Trichuris trichiura*, two *Entamoeba coli* and one *Endolimax nana*. In a previous study we found 56 per cent of our sprue patients infested with *Necator americanus* and 20 per cent with *Schistosoma mansoni*.

*Gastroscopic Findings.* No gastroscopic or sigmoidoscopic examinations were performed in these patients, but gastroscopic studies on sprue

patients have been carried out in Puerto Rico by Rodriguez-Olleros<sup>14</sup> and by Hernandez-Morales.<sup>15</sup> In cases of full-blown sprue, the former found atrophy of the gastric mucosa in nine out of 10 cases. In the remaining case, the examination proved unsatisfactory. Rodriguez-Olleros expressed the opinion that the atrophy of the gastric mucosa in pernicious anemia was more intense than in sprue. Of nine cases with the "incomplete syndrome," he found slight atrophy in only three cases. In the other six, there were "alterations of the gastric mucosa without, however, any definite characteristics." Of the third group of nine patients examined—with the "latent syndrome"—a normal mucosa was found in only three. It is of interest that hypertrophic gastritis was found in three of these last patients. Rodriguez-

TABLE IX  
Fat Content of the Stools  
(Method of Kayne, Lebner and Connor)

	No. of cases	% Solid in fresh feces	% Total fats in dried feces	Partition of fats—% Total fats				
				Split fats			Neutral fats	Unsap.
				Free acids	Soaps	Total		
Acute sprue before treatment	10	19.18	26.46	79.31	6.48	85.22		
Acute sprue, few days after folic acid	8	13.19	20.76	67.33	5.40	72.75		
Old sprue, years under liver therapy	5	19.05	17.71	66.30	8.12	74.42	19.99	4.89
Normal subjects, 13 samples	4	25.23	21.23	63.77	8.51	72.28	18.89	6.28

Olleros believes that "the atrophic gastritis that accompanies the full-blown syndrome of sprue appears during the height of development of the clinical picture and does not precede it."

Hernandez-Morales performed 61 gastroscopic examinations in 36 patients suffering from sprue, both during the stage of acute diarrhea and after treatment with liver extract. In 55 per cent of the patients, atrophic changes were observed in the gastric mucosa. Of 16 patients who were reexamined with the gastroscope after treatment, 10 (62 per cent) showed a normal gastric mucosa. Rectosigmoidoscopic examinations, also performed by Dr. Hernandez-Morales during the acute diarrheal stage, revealed several types of lesions, such as patches of atrophy, edema, friability, purpuric spots, and superficial inflammation.

*Roentgen Studies of the Intestinal Tract.* Because of the scarcity of film, roentgen examination of the intestinal tract was performed in only four cases, one showing definite segmentation and three showing coarsening of the mucosa. In 71 cases previously studied with Ruiz Cestero, a normal

feathery, herringbone appearance of the valvulae conniventes, with an even contour and normal size of the intestinal lumen, was demonstrated in 30 per cent of the cases, 70 per cent showing radiological evidence of "deficiency pattern." The stomach was found normal in 80 per cent, 20 per cent showing signs of gastritis. This study confirmed the opinion that in sprue, most of the roentgenological evidence of the disease is found in the small intestine, especially the jejunum.

*The Glucose Tolerance Curve.* The occurrence of a flat glucose tolerance curve, reported by Thaysen (1932) and by Hanes (1935) in non-tropical sprue and by Fairley in tropical sprue, has been corroborated by us. When the sprue patient ingests 1 gm. of glucose per kilo of body weight, the increase in blood sugar rarely goes above 40 mg. per 100 c.c.

In our original 40 cases (1938), only four patients (10 per cent) showed an increase of over 40 mg. per cent in their blood sugar after the oral administration of glucose. Unpublished data on 100 new cases showed that 20 per cent had an increase of over 40 mg. per cent. The discrepancies in the results obtained in these two series may be explained by the fact that liver extract had been administered prior to hospitalization, more often to patients of the latter series.

In our present group of cases, the glucose tolerance curve observed prior to treatment in 18 patients (table 10) showed an increase in blood glucose which varied from .3 to 32.5 mg. per cent. All patients studied, therefore, showed a flat glucose tolerance curve. Studies repeated from one to two months later during folic acid therapy showed that five of the 14 patients

TABLE X  
Glucose Tolerance  
1 Gm. per Kilo.  
Increase in Mg.

Case	Before Treatment	During Treatment	Time (Months)
1		41.2	2.0
2	13.5	15.9	1.0
3	16.6		
4	6.9	53.9	1.0
5	14.9	24.0	2.0
6	32.5	29.8	2.0
7	12.0		
8	.3	21.8	1.75
9	23.8	44.0	1.5
10	9.2	37.6	2.5
11	9.8	42.6	1.5
12	27.7	28.8	1.0
13		20.9	
14	9.4	45.0	1.25
15	18.7		
16	4.9		
17	18.8	12.6	1.0
18	16.2	41.9	1.0
21	14.6		
22	10.1		

now had a normal oral glucose tolerance curve, and that all but two of the patients had shown an improvement in their absorptive capacity for glucose. In cases 6 and 17 the glucose tolerance curves were lower two months and one month respectively, after the inception of treatment.

*Pathological Anatomy.* Reports of postmortem findings in cases of sprue are so meager in the medical literature and the findings are said to be

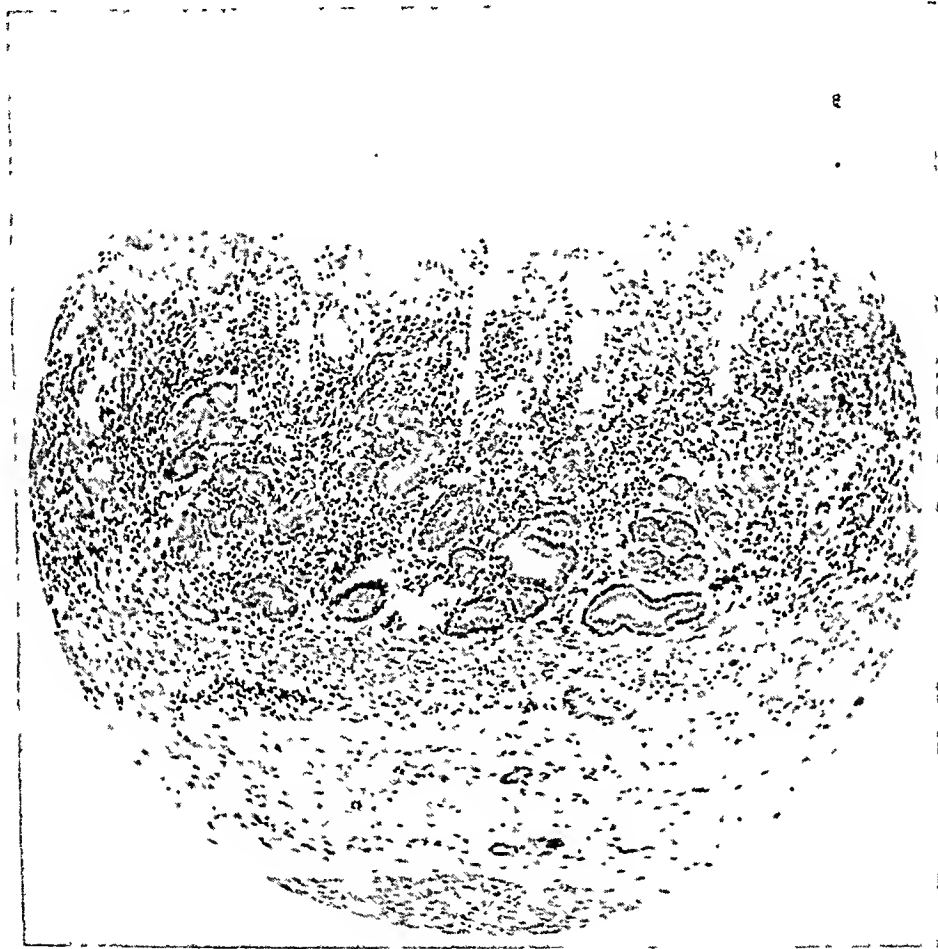


FIG. 2. Pyloric portion of the stomach. Despite the autolysis, the paucity of glands, their slight cystic dilatation, the colonic conversion of glands and the round cell infiltration are clearly visible. 80 X (Courtesy Dr. Koppisch).

so variable and inconstant that we have thought it advisable to summarize the findings in 16 autopsies performed by Koppisch\* at our School of Tropical Medicine.

In a total of 1356 autopsies performed from 1926 to 1943, sprue was encountered in 16. The body in all these cases was markedly wasted and the viscera were atrophied, especially the heart, spleen and liver. In all depots, the fatty tissues had undergone serous atrophy. The wall of the

\* Personal communication.

stomach and small intestine was thinner than normal in half the cases, that of the colon, in one third. The lingual mucosa was smooth, with atrophied papillae in about one third. All organs and tissues were very pale from anemia. The bone marrow in the middle third of the femur was of variable appearance: (a) red and diffusely hyperplastic; (b) pale and gelatinous but with red foci of activity, and (c) diffusely pale, semi-translucent and gelatinous. Microscopically, the three types corresponded, respectively, to

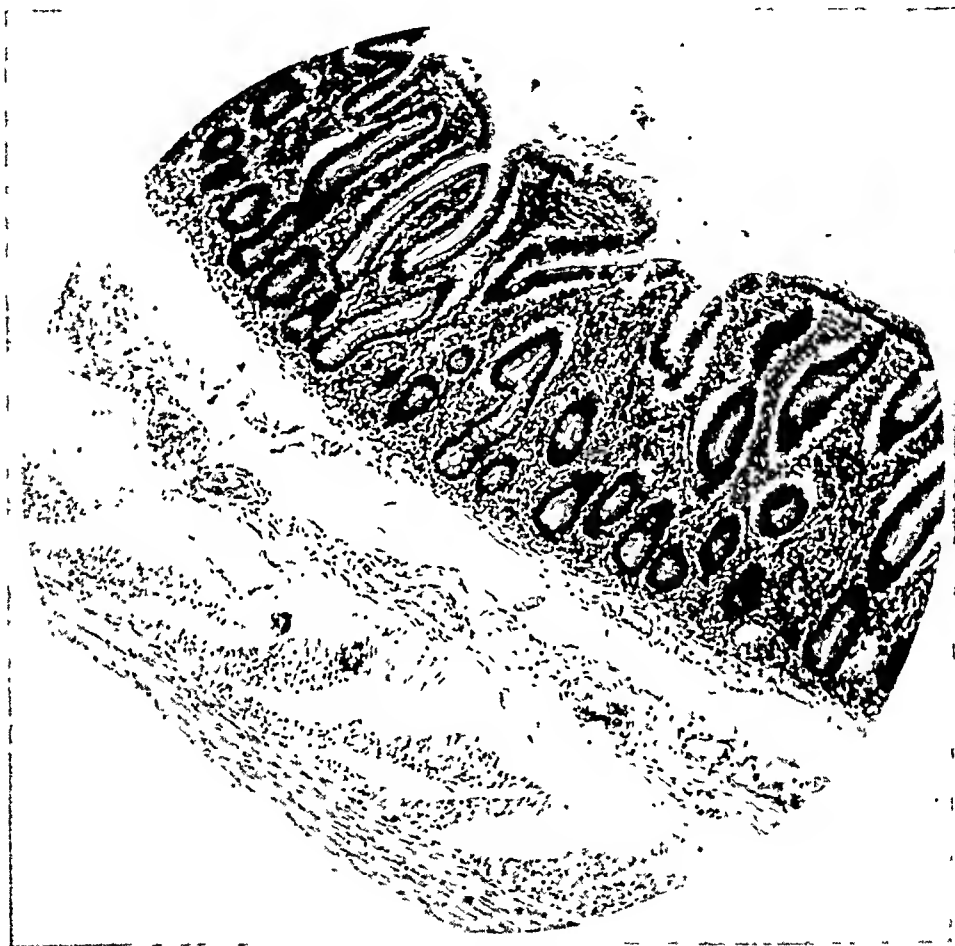


FIG. 3. Section of ileum showing broadening of villi and dense infiltration of propria with plasma cells and lymphocytes. Formalin was injected into abdominal cavity immediately after death. 80  $\times$  (Courtesy Dr. E. Koppisch).

diffuse hyperplasia of megaloblastic type, to foci of megaloblastic hyperplasia in an otherwise inactive marrow showing serous atrophy of the medullary fat, and to complete hematopoietic inactivity and far advanced serous atrophy of the medullary fat.

Other microscopic findings of interest were brown atrophy of the myocardium, atrophy of the malpighian corpuscles in the spleen; atrophy, hemosiderosis and edema of the liver; advanced depletion of lipoids in the supra-

renal cortex accompanied by cortical atrophy and occasional focal loss of tissue in the fasciculate zone, which became replaced by scars; and a marked reduction of spermatogenesis in the male. Atrophy of pancreatic acini was seen in one third and very slight interstitial fibrosis in two out of 15 cases. Findings in the gastrointestinal tract consisted of round-cell infiltration and hypervascularization of the subepithelial connective tissue of the tongue in all cases. The lingual mucosa showed atrophy in one half the cases, and

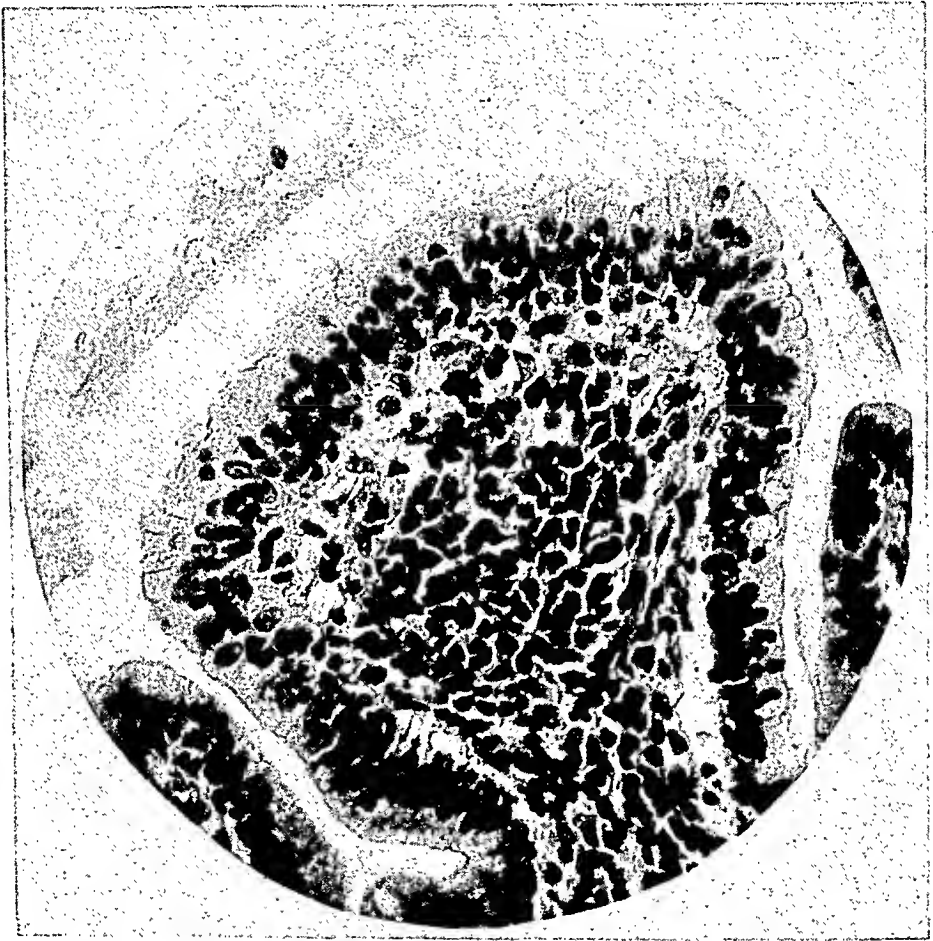


FIG. 4. Broadened villus with dense infiltration of propria with round cells. 360  $\times$  (Courtesy Dr. E. Koppisch).

zones of atrophy alternating with hyperplasia in the remainder. The gastric mucosa was moderately atrophied in half the cases, while there was chronic gastritis in all but three (figure 2). Distinct shortening and blunting of the villi of the small intestine was noted in half the cases (definitely not attributed to postmortem changes), accompanied by an increase in the number of plasma cells in the tunica propria (figures 3 and 4). The remaining cases presented no detectable abnormalities, except for occasional edema of

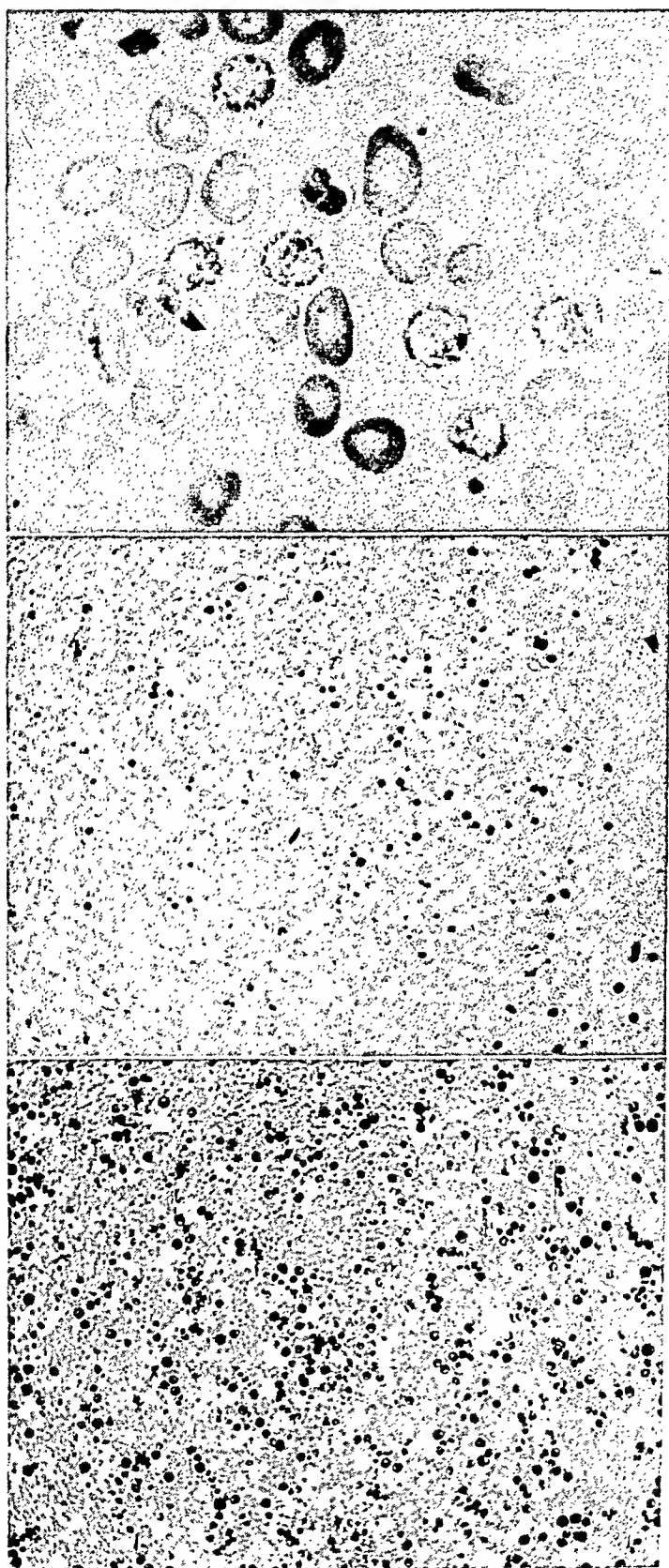


FIG. 5. A. Sternal marrow (aspiration) of sprue patient on admission. B. Sternal marrow one month later. Folic acid treatment. C. Reticulocyte response to folic acid on seventh day.

the submucosa. The colon was normal in only three cases. Acute colitis, in most instances mild, was found in seven, and a few non-specific ulcers in six. In three, the mucosa seemed thinner than normal, while in four there was atrophy of the muscle coats. The spinal cord was examined in only five cases. Combined degeneration was not found in any.

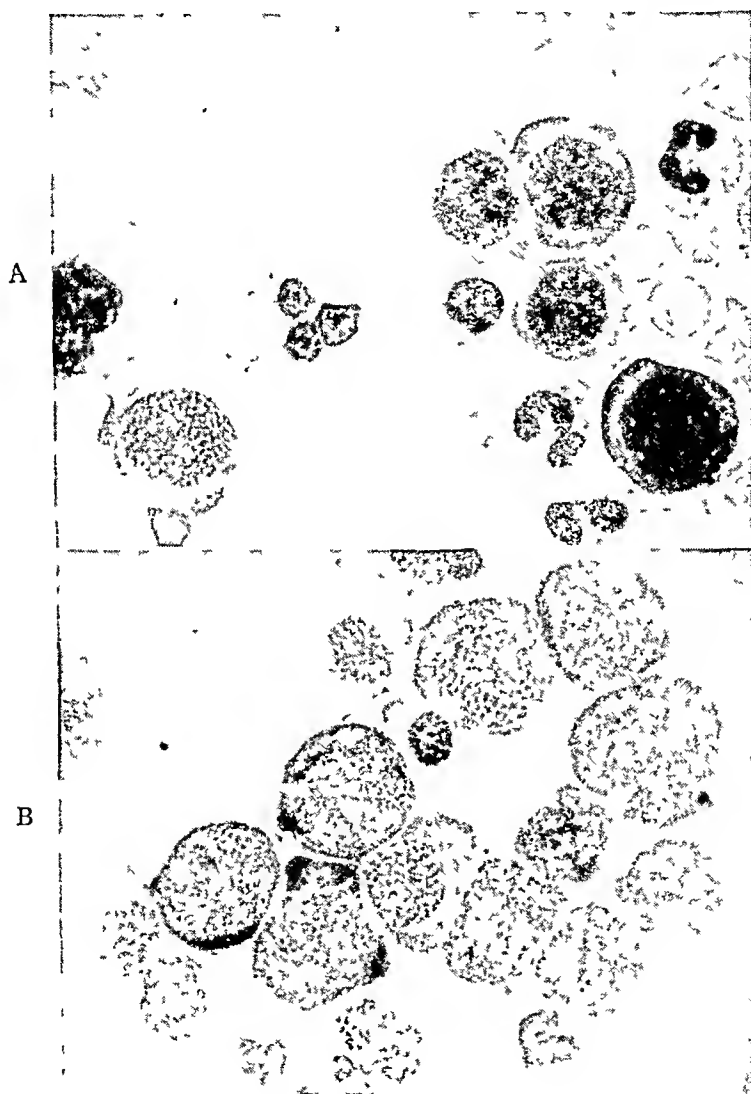


FIG. 6. A. Sprue—megaloblasts in sternal marrow. B. Sprue—erythroblastic arrest in sternal marrow.

The internal organs were small. The weight of the liver varied from 720 to 1,620 gm., with an average of 1,066 gm. (normal, 1,400 to 1,600 gm.); the heart weighed from 140 to 270 gm., with an average of 230 gm. (normal 280 to 300 gm.), and the spleen from 5 to 140 gm., with an average of 74.9 gm. (normal 125 to 150 gm.).

*Clinical and Hematological Response.* The clinical and hematological



response (table 11; figures 5 and 6) of sprue patients to folic acid, as already stated by other investigators, has been as striking and dramatic as that observed after parenteral liver therapy. The fact that folic acid is effective when given orally, even in the presence of diarrhea, makes this treatment less objectionable and exerts a favorable effect upon the patient's coöperation.

TABLE XI  
Folic Acid in Sprue  
Sternal Marrow

	Initial (22 cases)	Days after (18 cases)
Megaloblasts	12.9	1.9
Erythroblasts—early	11.1	4.6
Erythroblasts—late	9.9	16.6
Normoblasts	9.4	24.7
Granulocytic series	42.9	46.2
Lymphocytic series	7.7	5.1
Plasma cells	1.0	0.6
Megakaryocytes	0.1	0.0

Three or four days after the use of folic acid is started, the patient will usually volunteer the statement that he feels better. By this time the reticulocytes begin to appear in the peripheral blood, the tongue is less angry looking, a few new papillae are visible, gaseous distention is not so marked, the diarrhea is not so troublesome. The patient becomes interested in his surroundings, most especially in his meals. The appetite improves rapidly and it often becomes voracious.

We began using 50 mg. of folic acid daily in patients who were getting our "preliminary" sprue diet, which, as already stated, is poor in meat and meat products and contains no poultry, cheese, liver or yeast. Cases 1 and 2 exemplify the effect of this therapy.

The patient in *Case 1* was moribund when she was admitted to the hospital. She weighed only 58 pounds, of which no less than six or eight pounds were made up of edema fluid.

Her red blood cells numbered slightly more than a half million per cubic millimeter. The hemoglobin was 17 per cent (2.46 gm.). The mean cell volume was 150 cubic microns. The white blood cells numbered 1,500, and the platelets 80,000 per cubic millimeter. The sternal marrow showed only 5.6 per cent megaloblasts. On the fourth day of treatment the reticulocytes went up to 7 per cent and reached a maximum of 18 per cent on the fifth day. On this day the erythrocytes were 710,000 per cubic millimeter, the hemoglobin 2.4 gm., the mean cell volume 169 cubic microns and the platelets 60,000. The reticulocyte count diminished rather rapidly to reach almost the zero level on the nineteenth day, when the dose of folic acid was reduced to 10 mg. daily, and a full sprue diet, rich in animal protein and low in fats and carbohydrates was given. Again a slight reticulocytic response, reaching 6.2 per cent, occurred seven days later, which has persisted slightly above the zero level for more than three months.

The improvement in the red blood cells and hemoglobin progressed steadily, so that at the end of one month the erythrocytes were 2,370,000 per cubic millimeter,

the hemoglobin 8.1 gm. (56 per cent), and the mean cell volume 116 cubic microns. After two months of treatment the red blood cells were 2,634,000 per cubic millimeter, the hemoglobin 9.8 gm. (68 per cent), the mean cell volume 88 cubic microns, the leukocytes 3,200 and the platelets 120,000 per cubic millimeter.

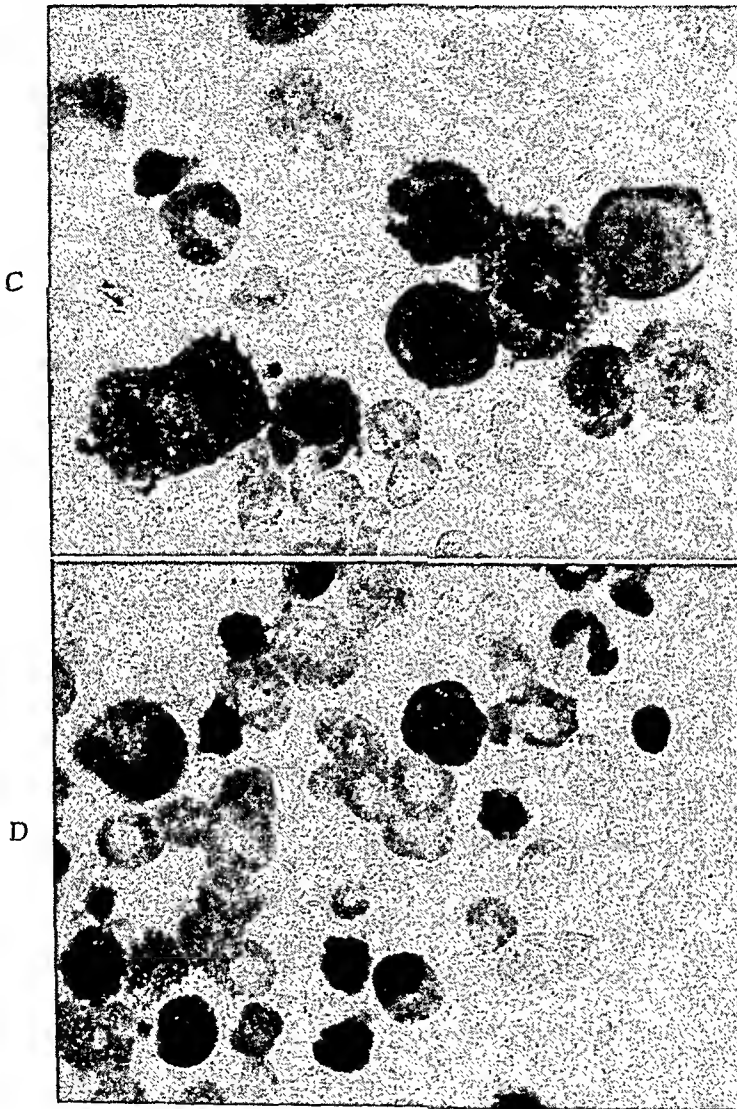


FIG. 6. C. Folic acid—maturation effect. D. Folic acid—normoblastic response.

The sternal marrow aspirated before treatment showed 5.6 per cent megaloblasts, 6.6 per cent early erythroblasts, 9.8 per cent late erythroblasts, 18.6 per cent normoblasts, the granulocytic series were 47.6 per cent and the lymphocytes 10.6 per cent with 1.2 per cent plasma cells. Five days after starting folic acid the normoblasts had gone up to 44.8 per cent, and the megaloblasts had almost completely disappeared (0.8 per cent), the early erythroblasts were 2.6 per cent and the late erythroblasts 14.4 per cent. So many normoblasts were present that the granulocytic series appeared relatively diminished, 35.2 per cent, and the lymphocytes 2.2 per cent.

The clinical improvement was dramatic. The patient who, on entry, could very well have exemplified the effect of one of the worst concentration camps in Europe or Asia, was now—after 2.5 months—a healthy looking woman weighing 105 pounds.

We admit that the reticulocytic response in this patient, with a peak of 18 per cent, was not what we could have expected considering the very low initial red blood cell count, but the critical, almost moribund state of this woman and a probable hypoplastic bone marrow might account for the sub-maximal response and for the persistence of moderate reticulocytosis. The reticulocytic curve as observed in the chart reminds us more of the reticulocytic response to iron therapy in hypochromic anemias, than of that observed in sprue treated with a potent liver extract.

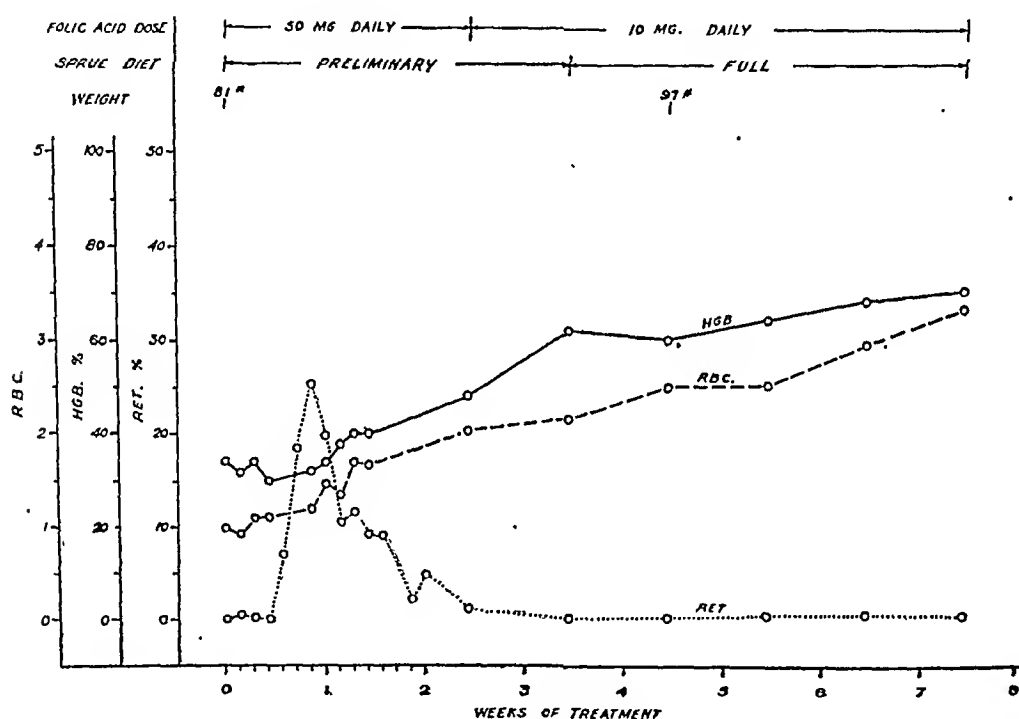


FIG. 7. Case 2.

In Case 2 (figure 7), the initial red blood cell count was 1,000,000 per cubic millimeter, hemoglobin 34 per cent (4.9 gm.), mean cell volume 160 cubic microns, leukocytes 2,600 and platelets 90,000 per cubic millimeter. On 50 mg. daily of folic acid and the preliminary sprue diet the reticulocytes rose to 7 per cent on the fourth day and 18.5 per cent on the fifth day, and reached a peak of 25.4 per cent on the sixth day of treatment. The reticulocytes came down to normal level at about the seventeenth day of treatment and stayed normal even after the institution of the full sprue diet.

There was also a progressive increase in the red blood cells and hemoglobin. At the third week of treatment the erythrocytes had gone up to 2,000,000, the hemoglobin to 48 per cent (6.96 gm.), the mean cell volume had decreased to 118 cubic microns, the leukocytes were 3,300 per cubic millimeter and the platelets 150,000 per cubic millimeter. On the seventh week of treatment the erythrocytes were over 3,000,000,

the hemoglobin 64 per cent (9.28 gm.), the mean cell volume 116 cubic microns, the white blood cells 3,700 and the platelets 180,000 per cubic millimeter.

The sternal marrow before treatment showed 12.2 per cent megaloblasts, 11.2 per cent early erythroblasts, 11 per cent late erythroblasts, 15.6 per cent normoblasts, the granulocytic series was 38.4 per cent, lymphocytes 10.2 and the plasma cells 1.4 per cent. Five days later the megaloblasts had come down to 1.2 per cent and the normoblasts had increased to 28.6 per cent. One month later there was a normal marrow present, with no megaloblasts, 3 per cent early erythroblasts, 5.5 per cent late erythroblasts, 16 per cent normoblasts, the granulocytic series were 60.5 per cent of the differential count and the lymphocytic series 15 per cent.

After having proved the effectiveness of a daily dose of 50 mg. folic acid, we tried giving 5 mg. daily together with the same inadequate or so-called "preliminary" sprue diet.

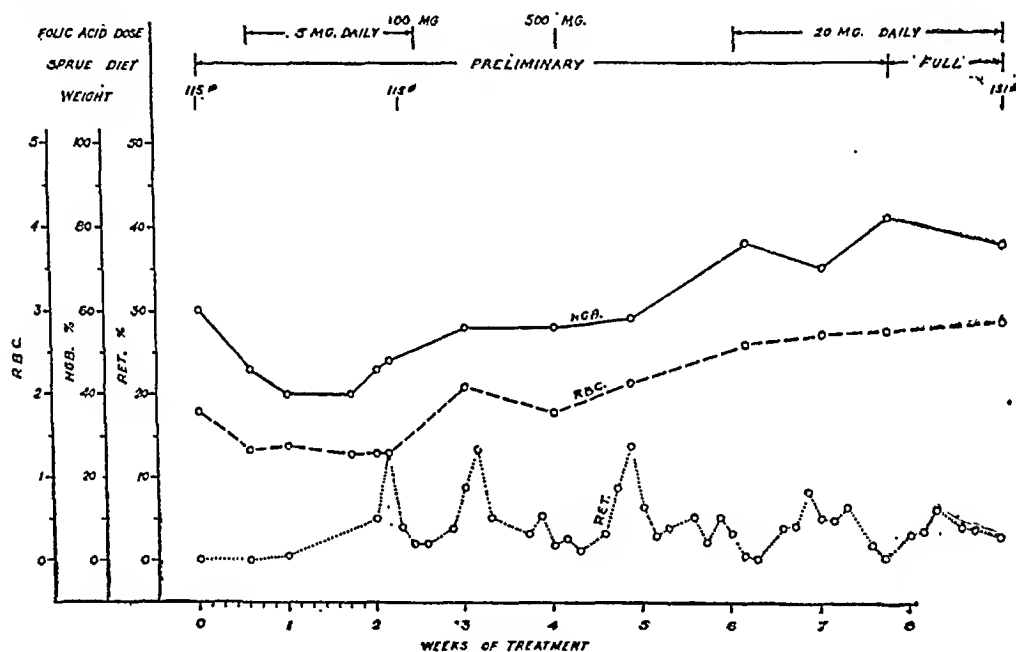


FIG. 8. Case 5.

In Case 5 (figure 8), the hemoglobin at the time of admission was 60 per cent (8.7 gm.). There were 1,780,000 red blood cells, a mean cell volume of 134 cubic microns, 7,300 leukocytes, 150,000 platelets per cubic millimeter and no reticulocytes in the peripheral blood. While the case was under study and before folic acid in 5 mg. daily doses was started, the hemoglobin had come down to 40 per cent (5.8 gm.), the erythrocytes to 1,380,000 per cubic millimeter, the leukocytes to 3,200, the platelets to 122,000 per cubic millimeter, while the mean cell volume remained at approximately the same level, 137 cubic microns.

Folic acid orally in 5 mg. daily doses was started and continued for 10 days. A slight peak in the reticulocyte count occurred on the eighth day, which came down to 2 per cent two days later. A slight increase in the hemoglobin took place, but the erythrocytes were apparently unaffected, as well as the clinical picture.

On the tenth day a single dose of 100 mg. of folic acid was given, which brought the reticulocytes up to 13.4 per cent five days later, with very slight improvement in hemoglobin and red blood cells. A larger single dose, 500 mg. of folic acid, was then given 10 days later, which again brought about a reticulocyte rise of 13.6 per cent in

five days. The subsequent administration of 20 mg. of folic acid daily with the "preliminary" sprue diet at first and then with full sprue diet, maintained a persistent moderate reticulocytosis for several weeks.

At the end of the observation period of two months, the patient showed marked improvement, and had gained 16 pounds. The erythrocytes were 2,860,000, the hemoglobin 75.8 per cent (10.8 gm.), the leukocytes 5,300, platelets 140,000 per cubic millimeter, and the mean cell volume 13.6 cubic microns. The sternal marrow showed a normal differential count of nucleated elements.

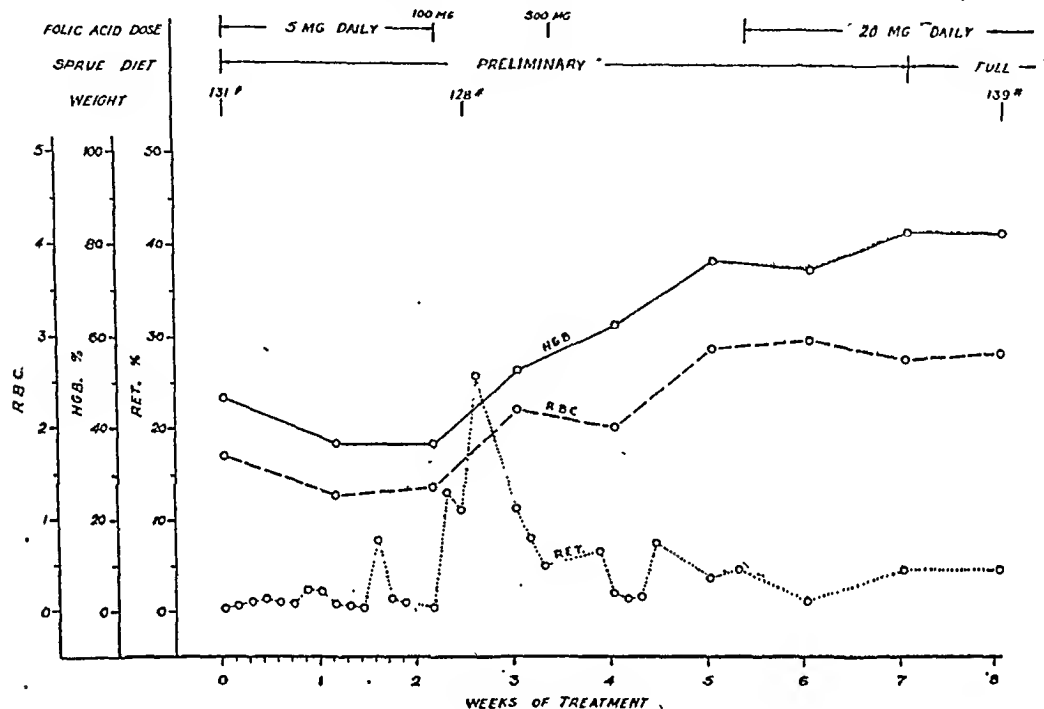


FIG. 9. Case 6.

In *Case 6* (figure 9), folic acid was also given, 5 mg. daily for 12 days, a single dose of 100 mg. on the thirteenth day, another single dose of 500 mg. on the twenty-third day, followed in two weeks by 20 mg. daily doses, until the end of the observation period. Again a 5 mg. daily dose proved insufficient to produce a maximal reticulocytic response. The reticulocytes rose only to 7.4 per cent. The single dose of 500 mg. was followed in five days by a reticulocytosis of 25.4 per cent, and the dose of 500 mg. with a lower peak of 7 per cent. After the institution of small daily doses and full sprue diet a moderate reticulocyte count persisted for several weeks. There was no noticeable hematological response, and very slight if any clinical improvement with daily doses of 5 mg.

At the end of the observation period of two months, the erythrocytes which originally numbered 1,600,000 had gone up to nearly 3,000,000, the hemoglobin from 46 per cent (6.67 gm.) to 82.4 per cent (11.7 gm.) and the leukocytes from 1,700 to 3,200 per cubic millimeter.

The sternal marrow showed only moderate changes with the administration of 5 mg. daily. A count of 12 per cent megaloblasts came down to 5.2 per cent five days later, the early erythroblasts remained the same, 14.2 per cent, the late erythroblasts went from 9.6 per cent to 24.8 per cent, and the normoblasts from 6.6 to 18.8 per cent. The granulocytic series were reduced from 42 to 28.4 per cent and the

lymphocytic series from 15.6 to 8.2 per cent. The marrow examined at the end of the observation period was practically normal, with only 0.2 per cent megaloblasts; the erythrocytic series comprising 26 per cent of the total differential counts, the granulocytic series 60.2 per cent and the lymphocytic series including plasma cells and megakaryocytes, 13.8 per cent.

*Case 7*, who also received daily doses of 5 mg., showed very slight effect in the nucleated elements of the sternal marrow while receiving this dose. The initial counts revealed the presence of 7.8 per cent megaloblasts, 7.2 per cent early erythroblasts, 9.6 per cent late erythroblasts, 9.8 per cent normoblasts, a granulocytic series of 60 per cent and lymphocytic elements of 5.6 per cent. Four days later, the megaloblasts were 6 per cent, the early erythroblasts 5.6 per cent, late erythroblasts 16 per cent, normoblasts 14 per cent, while the granulocytes were 54 per cent and the lymphocytes 4.4 per cent.

The eight patients who received 20 mg. folic acid daily with preliminary sprue diet, showed adequate hematological and clinical response. The one who received a single dose of 200 mg. of folic acid had an initial erythrocytic count of 3,000,000 and therefore did not show any definite evidence of hematopoietic stimulation, but undoubtedly responded better to daily doses of 20 mg. especially when the full sprue diet was added.

The following two cases (12 and 16), who on admission had similar red blood cell counts and hemoglobin determinations, will serve to evaluate the efficacy of folic acid in the presence of an adequate sprue diet as contrasted with an inadequate diet.

*Case 12* (figure 10) had an initial count of 800,000 red blood cells per cubic millimeter and 19 per cent (2.75 gm.) of hemoglobin. When folic acid was started

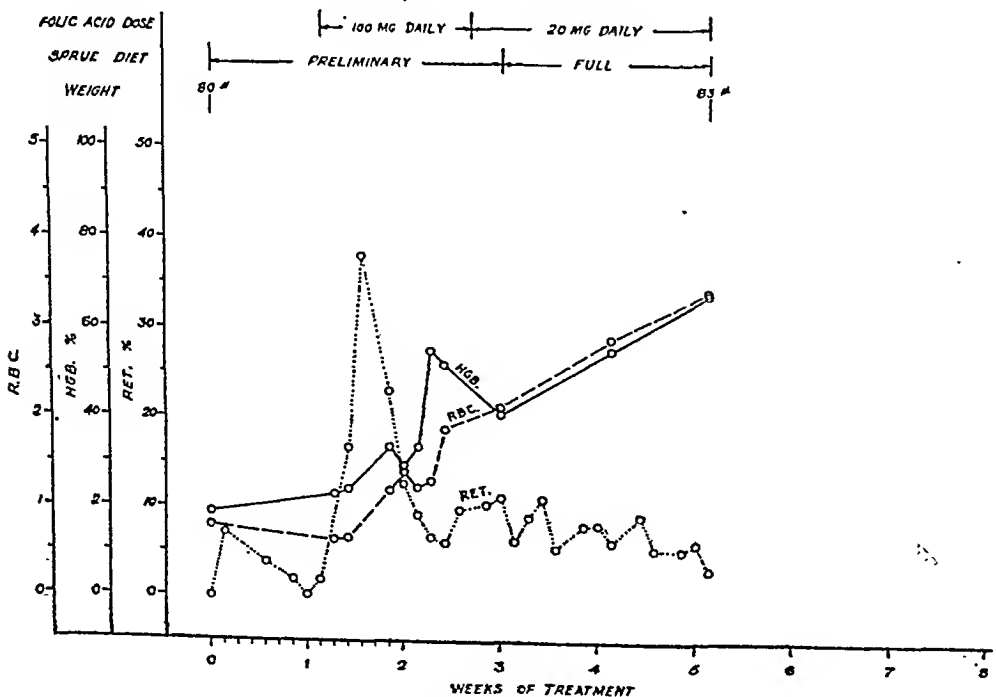


FIG. 10. Case 12.

in doses of 100 mg. daily, the reticulocytes in her peripheral blood were only 2 per cent and the red blood cells 650,000 per cubic millimeter, although there had been a spontaneous reticulocytosis up to 7.2 per cent during the preliminary period of study. A marked reticulocytic increase appeared two days after folic acid was started and reached its peak of 38 per cent on the third day of treatment. The reticulocytes in the peripheral blood remained between 3 and 11.2 per cent for about four weeks, even though the dose of folic acid had been reduced to 20 mg. daily on the tenth day and a full sprue diet was allowed. At the end of the observation period of five weeks, the red blood cells were 3,530,000 per cubic millimeter, the hemoglobin 67.8 per cent (9.6 gm.), reticulocytes 4 per cent, leukocytes 4,000 and the mean cell volume 101 cubic microns. The platelets, which originally numbered 96,000, went up to 112,000 per cubic millimeter.

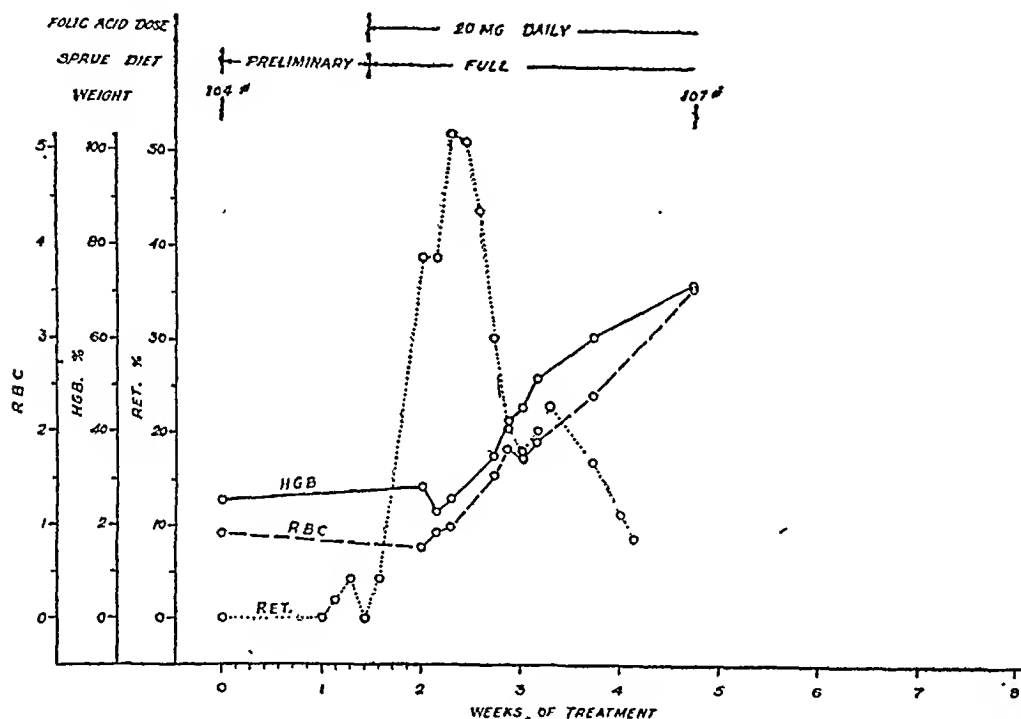


FIG. 11. Case 16.

In *Case 16* (figure 11) the blood picture on entry was similar to that in the preceding case. This patient was put on a full sprue diet with 20 mg. of folic acid daily. The reticulocytic response was most marked. Four days later the reticulocytes were 38.8 per cent and reached a peak of 51.8 per cent on the seventh day of treatment, coming down gradually to 8.6 per cent on the twenty-first day. The red blood cells went from 930,000 per cubic millimeter to 3,550,000 in three weeks, the hemoglobin from 25.6 per cent (3.6 gm.) to 71.8 per cent (10.2 gm.), the leukocytes from 1,400 to 4,400 per cubic millimeter, the platelets from 90,000 to 142,000 per cubic millimeter and the mean cell volume was reduced from 129 to 101 cubic microns.

*Case 20* (figure 12) was given 10 mg. of folic acid daily, with a full sprue diet. The initial erythrocytic count was 1,750,000 per cubic millimeter, hemoglobin 54 per cent (7.7 gm.), leukocytes 2,800, platelets 216,000 per cubic millimeter and the mean cell volume 165 cubic microns. A peak of 27.2 per cent in the reticulocytic count occurred on the fifth day of treatment, which gradually came to normal level on or

about the twenty-fourth day. The red blood cells and hemoglobin went up rapidly to reach almost normal figures in about three weeks.

The study of these last two cases seems to prove that in the presence of an adequate diet, 10 mg. daily of folic acid will give as good results, if not better, than 100 mg. daily with a diet deficient in animal proteins.

Summaries of the histories and laboratory reports of a few of the representative cases are presented:

*Case 1.* This 30 year old white Puerto Rican female was admitted on November 31, 1945, complaining of marked weakness and diarrhea of nine months' duration.

According to the patient, she had eaten a fairly well balanced diet (?) and had apparently been well until about a year ago, when she began to notice progressive

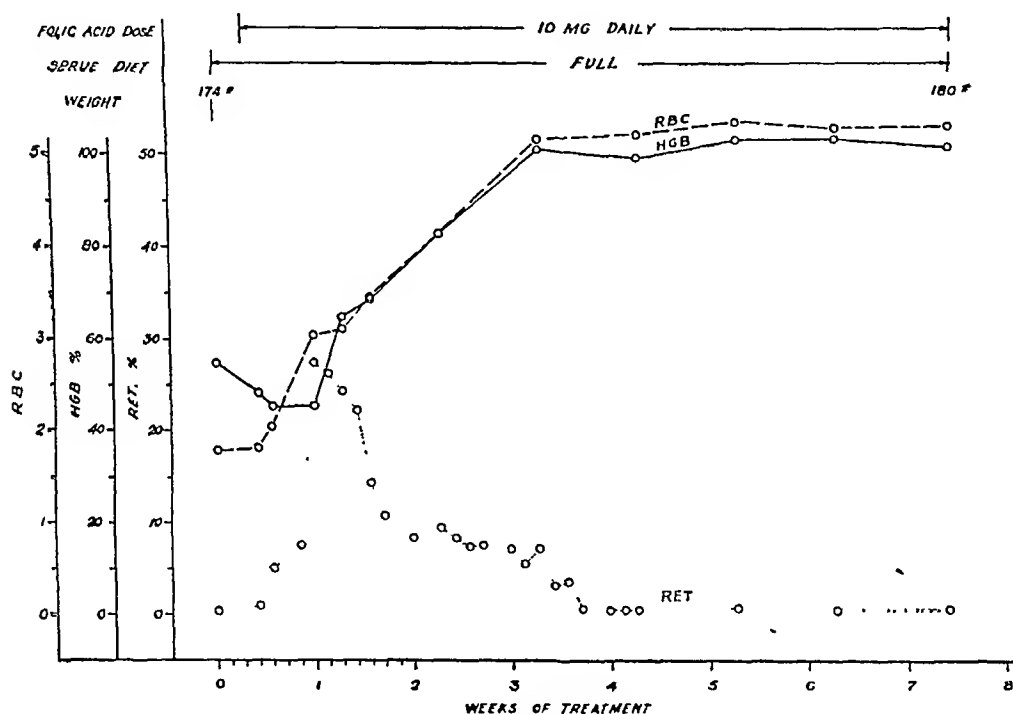


FIG. 12. Case 20.

weakness and loss of weight. Three months later, weakness had progressed to a point where patient could walk only a few steps, and she developed a severe diarrhea. At this time (nine months ago) she entered one of the small municipal hospitals, where she was treated up to three days ago, when the patient was transferred to the Bayamon District Hospital. From the latter institution the patient was referred to us. The stool is described as being watery, greenish turning into yellow and white at times, abundant, foamy with mucus and some tenesmus; marked flatulence, but no blood. Burning sensation in the tongue developed with the onset of diarrhea. Before entry, she had received one blood transfusion about four months ago and 12 injections of crude liver extract, the last one administered two months ago.

The patient had not menstruated in the preceding nine months. Before the onset of symptoms she had weighed about 100 pounds; on admission her weight was 58 pounds—a loss of 42 per cent.



*Physical examination:* The physical examination revealed a very pale, cachectic, white woman apparently 15 years older than the stated age, lying quietly in bed in an almost moribund state. Temperature was 98°, pulse 104, respirations 22. Physical examination was negative, except for the evident anemia and malnutrition. There was a soft grade 2 systolic murmur at the apex. The abdomen had a doughy feeling. The skin of the arms and legs was dry and scaly (ichthyosis). The tongue was smooth and pale. There was moderate cheilitis. The gums were spongy and pyorrheic. Two upper teeth were missing. Slit-lamp examination revealed normal limbic vessels and only moderate thickening of the conjunctival epithelium.

*Blood* (December 1, 1945): Erythrocytes 650,000 per cu. mm.; hemoglobin 17 per cent (2.46 gm. per 100); mean cell volume 130 cubic microns; white blood cells 1,500; platelets 80,000 per cubic mm. and no reticulocytes. The differential count showed: lymphocytes 57 per cent; neutrocytes 43 per cent, of which 44 were segmented, 1 per cent stabs, and there were 2 per cent normoblasts.

*Bone marrow:* The sternal bone marrow on the day of entry showed 5.6 per cent megaloblasts; 6.6 per cent early erythroblasts; 9.8 per cent late erythroblasts and 18.6 per cent normoblasts. The erythrocytic series was, therefore, 40.6 per cent. The granulocytic series was 47.6 per cent and the lymphocytic series (including plasma cells, of which there were 1.2 per cent) 11.8 per cent.

*Blood serology:* Kahn, 4 plus. Kolmer and Kline reactions also positive on entry. Three weeks later the Kahn test remained positive. Hanger cephalin flocculation test was 4 plus on entry.

*Stools:* Repeatedly negative for intestinal parasites. Urobilinogen determinations, 10 to 15 mg. in 24 hours. The following table shows the study of the fat content of the feces:

Days of treatment	Character of feces	% Solids in fresh feces	% Total fats in dried feces	Partition of fats—% Total fats				
				Digested fats			Neutral fats	Unsaponifiable
				Free acids	Soaps	Total		
1	Diarrhea	12.3	39.82	78.11	3.57	81.67	15.33	2.99
2	Diarrhea	10.9	38.87	62.46	22.47	84.93	10.33	4.75
9	Diarrhea	7.2	24.19	65.43	11.37	76.80	20.53	2.67
15	Diarrhea	5.9	23.38	65.03	11.16	76.19	22.62	1.19
21	Diarrhea	6.2	26.84	85.12	4.17	89.29	8.98	1.74
41	Diarrhea	10.4	29.10	83.71	2.57	86.28	9.18	4.64
51	Very soft but solid	9.3	23.19	82.78	3.89	86.67	10.93	2.40

Roentgenogram of the chest negative. The patient was too sick for gastrointestinal investigation.

*Blood chemistry* (February 6, 1945): Serum proteins 5.88, serum albumin 4.55; serum globulin 1.33.

*Biophotometric studies:* One month after admission studies showed a low curve which began at 15, went up to 24 in five minutes and finished at 58 at the end of 10 minutes. (Normal curve for this apparatus begins at 55, goes up to 88 in five minutes and ends in 100 at 10 minutes.)

*Folic acid:* Folic acid was started on December 1, 1945, twenty-four hours after admission to the hospital, in 50 mg. daily doses, administered per os (figure 13). Three days later there was slight improvement in the patient's appetite and in the number and character of the stools, and a reticulocyte increase of 7 per cent was seen on the fourth day. From then on, and in spite of the preliminary sprue diet, the

patient responded both clinically and hematologically. Five days following folic acid administration, the red blood cells were 710,000 per cu. mm.; hemoglobin 17 per cent (2.36 gm. per 100); mean cell volume 169 cubic microns; platelets 60,000 per cu. mm., and the reticulocytes had gone up to 18 per cent. The improvement in the red blood cells and hemoglobin progressed steadily, so that at the end of one month (January 1, 1946) the erythrocytes were 2,370,000; hemoglobin 56 per cent (8.1 gm. per 100), and the mean cell volume 116 cubic microns. The reticulocyte response, as already stated, reached a peak on the fifth day of 18 per cent; it was 13 per cent next day and on successive days the figures were 11.6 per cent, 12.4 per cent, 9 per cent, 4.2 per cent, 4 per cent and 2.8 per cent, diminishing to 0.2 per cent on the nineteenth day, when the dose of folic acid was diminished to 10 mg. daily, while the patient

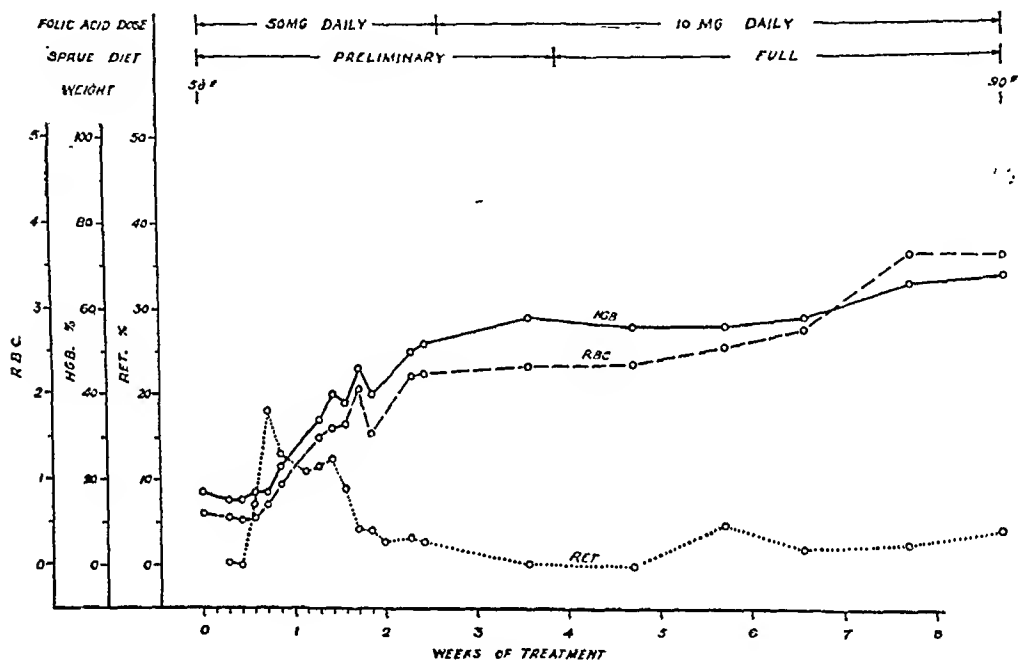


FIG. 13. Case 1.

was being kept on the meat free diet. On December 28, 1945, the diet was changed to a full sprue diet which is rich in animal proteins and low in fats and carbohydrates, the folic acid being continued at the same dose of 10 mg. daily. Seven days later there was observed again a moderate reticulocyte response which ranged between 0.2 per cent to 6.2 per cent during the entire period of observation which has lasted for three months.

On February 1, 1946 after two months of treatment, the erythrocytes had gone up to 3,630,000, the hemoglobin 68 per cent (9.86 gm. per 100), the mean cell volume 88 cubic microns, the white blood cell count, which originally was 1,500, was up to 2,100 on the sixth day. In a month it was 3,200, in two months it was 5,600 per cu. mm. On admission the differential count did not reveal any eosinophilic nor any juvenile granulocytes, and the lymphocytes were, as already stated, 57 per cent. With the progressive increase in the number of leukocytes there occurred a diminution in the number of lymphocytes and at the same time eosinophiles appeared in the peripheral blood, as well as juvenile granulocytes. The normoblasts in the peripheral blood were from 1 to 3 per cent during the first few days; a single megaloblast was encountered on the sixth day of treatment. Six days following the institution of folic

acid therapy, there were 40 per cent lymphocytes and 60 per cent granulocytes, of which 46 per cent were segmented, 4 per cent stabs, 7 per cent juveniles and 3 per cent eosinophiles. At the end of the first month the lymphocytes had gone down to 38 per cent and the granulocytes were 62 per cent, of which 49 were segmented, 3 per cent stabs, 2 per cent juveniles and 7 per cent eosinophiles. At the end of two months the lymphocytes were 21 per cent and the granulocytes 79 per cent, made up of 54 per cent segmented, 2 per cent stabs, 9 per cent juveniles, 11 per cent eosinocytes and 3 per cent basocytes. The platelets on entry were 80,000 per cu. mm. There was an apparent diminution of the platelets during the first six days following folic acid therapy, but from then on the platelets gradually increased in number, being 136,000 one month later and 210,000 at the end of the observation period.



FIG. 14. (Left) Case 1 on admission; weight 58 pounds. Edema of legs and face. (Right) Same case, two and one-half months after treatment with folic acid; weight 105 pounds.

The bone marrow showed definite changes of the so-called maturation effect similar to that observed following parenteral liver therapy. Five days after the institution of the treatment, the megaloblasts had gone down to 0.8 per cent and the early erythroblasts to 2.6 per cent, the late erythroblasts had increased to 14.4 per cent, and the normoblasts to 44.8 per cent. The erythrocytic series went up to 62.6 per cent and the granulocytic and lymphocytic series diminished to 35.2 per cent and 2.2 per cent respectively.

The clinical improvement was almost spectacular (figure 14). The appetite had become voracious. Six days after the administration of folic acid was instituted, the tongue already showed scattered papillae and it was not as pale. The stools had become semi-solid. Twenty-two days later, the tongue was absolutely normal, having

become magenta in color. This magenta coloration of the tongue was disappearing by the thirty-eighth day of treatment. The stools became hard three weeks after full sprue diet was instituted and remained in the same state thereafter. The weight had increased from 58 pounds to 89 pounds at the end of the first month, and to 105 pounds at the end of 2.5 months, a gain of 45 pounds or double the patient's weight. The amenorrhea has now persisted for over a year.

Note: Because of the patient's critical condition on entry, some of the laboratory tests could not be done.

*Case 12.* A 19 year old white female was admitted to the hospital with the chief complaint of epigastric pain and diarrhea of two years' duration. She was referred from the Municipal Hospital of Rio Piedras with the diagnosis of sprue.

The patient stated that she was doing nicely and was on an adequate diet up to two years previously, when she began to develop anorexia, diarrhea and vomiting, also flatulence following fatty meals. Vomiting is said to have followed every meal. The stools are described as tarry, watery, white on one or two occasions, and foamy, with mucus but no blood. A few days later post-prandial epigastric pain developed; pain is said to be continuous and nonradiating.

About one month after onset of symptoms, patient began to get weak and pale and arrived at the Municipal Hospital in Rio Piedras in very poor condition. While in the hospital she received liver injections for 10 days and one blood transfusion. She was discharged after 23 days of treatment, somewhat improved, only to relapse two weeks later while at home, returning to her previous condition. In this plight, she was admitted to this hospital. The family, social and past histories are irrelevant, except that the patient had had malaria one and a half years ago, and had waded a stream at Aguas Buenas, which is known to be infested with *Schistosoma mansoni*.

*Physical examination:* Temperature 101° F., pulse 118 per minute, respirations 24, blood pressure 100 mm. Hg systolic and 50 mm. diastolic. A fairly well developed, malnourished, markedly pale white girl, obviously weak, bed-ridden and not in acute distress. The tongue was very pale, but papillae were present except at the margins, where there was definite glossitis. There was a soft blowing systolic murmur, grade 2, over the pulmonic area. The extremities showed lack of subcutaneous fat but no edema.

*Neurological examination:* Negative.

There were no ocular or cutaneous manifestations of vitamin deficiencies. The weight on entry was 80 pounds.

*Blood:* The red blood cells on admission (January 29, 1946) were 800,000 per cu. mm.; hemoglobin 19 per cent—2.75 gm.; mean cell volume 118 cubic microns; white blood cells 2,650 per cu. mm.; platelets 96,000 per cu. mm.; no reticulocytes.

*Bone marrow:* Showed 22 per cent megaloblasts, 12.8 per cent early erythroblasts, 12.6 per cent late erythroblasts, 2.4 per cent normoblasts. The erythrocytic series, therefore, was 49.8 per cent. The granulocytic series was 42.4 per cent and the lymphocytic series 7.8 per cent.

*Serology:* Negative.

*Blood chemistry:* Revealed non-protein nitrogen 22 mg. per cent, urea nitrogen 8.33 mg. per cent, glucose 101.5 mg. per cent, cholesterol 144.2 mg. per cent, inorganic phosphorus 3.7 mg. per cent, calcium 9.6 mg. per cent, phosphatase 2.6 Bodansky units, icteric index 8.64, van den Bergh reaction direct delayed, total serum proteins 6.69 gm. per cent, serum albumin 4.92 gm. per cent, and serum globulin 1.77 gm. per cent.

*Hanger cephalin flocculation test:* 4 plus on entry, January 29, 1946. Seven days later, it was reported as 3 plus.

*Gastric analysis:* Under histamine stimulation was 0°, 0°, 0°, 18° and 10° in the five specimens, respectively.

*Glucose tolerance curve:* On entry, January 29, 1946, was 92 mg. per cent, 113 mg. per cent, 119.7 mg. per cent, 97.6 mg. per cent and 97.1 mg. per cent, an increase of 27.7 mg. per cent. One month later, the figures were 101 mg. per cent, 129.8 mg. per cent, 113 mg. per cent, 109.9 mg. per cent and 88.9 mg. per cent, an increase of 28.8 mg. per cent.

*Biophotometric investigation:* Dark adaptation curve started at point 23 and finished at point 64 (normal curve begins at point 55 and ends at point 100).

Roentgenogram of the chest was negative.

The sputum was repeatedly negative for tubercle bacilli.

*Stools:* Revealed only the presence of *Trichuris trichiura*. The fat content was as follows:

Character of feces	% Solids in fresh feces	% Total fats in dried feces	Partition of fats—% Total fats				
			Digested fats			Neutral fats	Unsaponifiable
			Free acids	Soaps	Total		
Diarrhea	7.61	8.56	69.86	8.22	78.08	16.99	4.93

*Folic acid:* (Figure 10). The patient was given a preliminary diet which consists mainly of rice and beans and root vegetables, with very little meat (not over one half pound of meat and one egg a week). During the observation period, while various diagnostic investigations were being made, there was a spontaneous reticulocytosis of 7.2 per cent, which disappeared two days later. Reticulocytes numbered only 0.2 per cent in the peripheral blood when folic acid was started. One hundred mg. of folic acid were given daily for 10 days. Three days later, the reticulocytes had gone up to 38 per cent, gradually coming down to 9.8 per cent on the sixteenth day of treatment. At the end of the week the red blood cells had gone up to 1,870,000, the hemoglobin was 50.2 per cent (7.0 gm. per 100), mean cell volume had increased to 160 cubic microns, white blood cells were 4,700. Folic acid was diminished to 20 mg. daily and a full sprue diet, high in animal proteins, low in fats and carbohydrates, was instituted on the tenth day. A new peak of reticulocytes did not occur, but there persisted a moderate increase which varied from 2 to 11.2 per cent for nearly a month. At the end of the first month of treatment, the clinical and hematological improvement was striking. The weight had gone up to 89 pounds. The appetite was voracious. The tongue was normal. The gastrointestinal disturbances had subsided and the blood picture showed a red blood cell count of 3,530,000, hemoglobin 67.8 per cent (9.6 gm. per 100 c.c.), the mean cell volume had decreased to 101 cubic microns, the white blood cells 4,600, reticulocytes 4 per cent and the platelets had gone up to 112,000 per cu. mm.

*Case 15.* A 56 year old white male admitted with the chief complaint of weakness and attacks of diarrhea of one and a half years' duration.

He felt well and was eating a well balanced diet until one and a half years ago when he noticed numbness of the fingers and toes. At about the same time he developed diarrhea. The stools were described as watery and whitish, from five to 15 in 24 hours. The diarrhea was accompanied by generalized abdominal pain and flatulence. There was also a burning sensation in the mouth and anus. During the first attack of diarrhea, which lasted for about a year, he received injections of vitamins. Since then he has had periods of constipation alternating with short episodes of diarrhea. Two nights before entry the diarrhea started again. The numbness of the toes and fingers progressed gradually, so much so that he had great difficulty

in walking unaided. He had lost about 30 pounds. He had never received liver.

The family history was irrelevant. He was married and was the father of 13 children. He did not smoke or use liquor and drank four cups of coffee daily.

*Physical examination:* On physical examination the patient was found to be a fairly well developed, rather poorly nourished elderly male, not in acute distress. His temperature was 98.6° F., pulse 80 per minute, respirations 20 and blood pressure 102 mm. Hg systolic and 74 mm. diastolic. The physical examination was essentially negative, except for the anemia, the loss of weight, the glossitis and the various signs and symptoms of combined system disease. There was moderate incoördination, ataxia, more marked in the lower extremities, hyperactive reflexes, marked bilateral patellar clonus, positive Romberg, absent vibratory sensation in the long bones of both legs and positive Babinski.

*Differential diagnosis:* The possibility of cerebrospinal syphilis was quickly discarded, since both the blood serum and the spinal fluid reacted normally and Argyll Robertson pupil was absent. A differential diagnosis between pernicious anemia with combined cord degeneration and sprue was very difficult.

*Blood:* The blood picture on entry (January 29, 1946) showed: red blood cells 2,830,000, hemoglobin 90 per cent (13.05 gm. per 100), white blood cells 5,350, mean cell volume 102 cubic microns.

*Bone marrow:* The bone marrow showed megaloblasts 7.4 per cent, early erythroblasts, 9.2 per cent, late erythroblasts 9.8 per cent and normoblasts 8 per cent, the granulocytic series being 60.2 per cent and the lymphocytic elements, including plasma cells and megakaryocytes were 5.4 per cent.

*Gastric analysis:* The gastric analysis revealed a histamine-resistant achlorhydria. A delayed rennin reaction and pepsinogen were present.

*Stools:* Negative for parasites. The study of the fat content was as follows:

Days of treatment	Character of feces	% Solids in fresh feces	% Total fats in dried feces	Partition of fats—% Total fats				
				Digested fats			Neutral fats	Unsaponifiable
				Free acids	Soaps	Total		
1	Solid but very soft	20.90	50.99	81.95	4.91	86.86	9.30	3.85
6	Solid	29.58	45.58	67.84	14.21	82.05	17.95	

*Glucose tolerance curve:* The glucose tolerance curve after 1 gm. of glucose per kilo of body weight, showed an increase of only 16.7 mg. per cent.

*Basal metabolic rate:* plus 12.5 per cent.

*Blood chemistry:* Non-protein nitrogen 33.8 mg. per cent, urea nitrogen 8.26 mg. per cent, glucose 90.1 mg. per cent, cholesterol 131.6 mg. per cent, phosphorus (inorganic) 3.3 mg. per cent, phosphatase 3.33 Bodansky units, calcium 8.8 mg. per cent, serum proteins 6.82 gm. per cent, of which 3.61 gm. was albumin and 3.21 globulin.

*Roentgenologic investigation:* The gastrointestinal tract showed coarsening of the mucosal folds of the small intestine, but no definite segmentation.

*Biophotometric investigation:* Showed a curve which began at point 22, gradually rising to finish at point 73 at the end of 10 minutes. (The normal curve begins at point 55 and ends at point 100.)

The patient was given folic acid 20 mg. daily (figure 15). At the same time he was kept under the preliminary sprue diet which is approximately the same diet that peasants or "jibaros" receive at their homes.

A moderate reticulocytic response was observed, which reached its peak of 11.2 per cent on the tenth day of treatment. The clinical and hematological picture exhibited a gradual but progressive improvement so that at the end of the first month the red blood cells had gone up to 3,200,000, the hemoglobin to 92 per cent (13.2 gm. per 100), the white blood cells to 7,200 and the platelets, which were normal on entry, remained unaffected. The sternal bone marrow one month after the institution of folic acid therapy showed only 1.2 per cent megaloblasts and 3.4 per cent early erythroblasts, 20 per cent late erythroblasts and 26.8 per cent normoblasts. A definite maturation effect had occurred. The granulocytic series had gone down

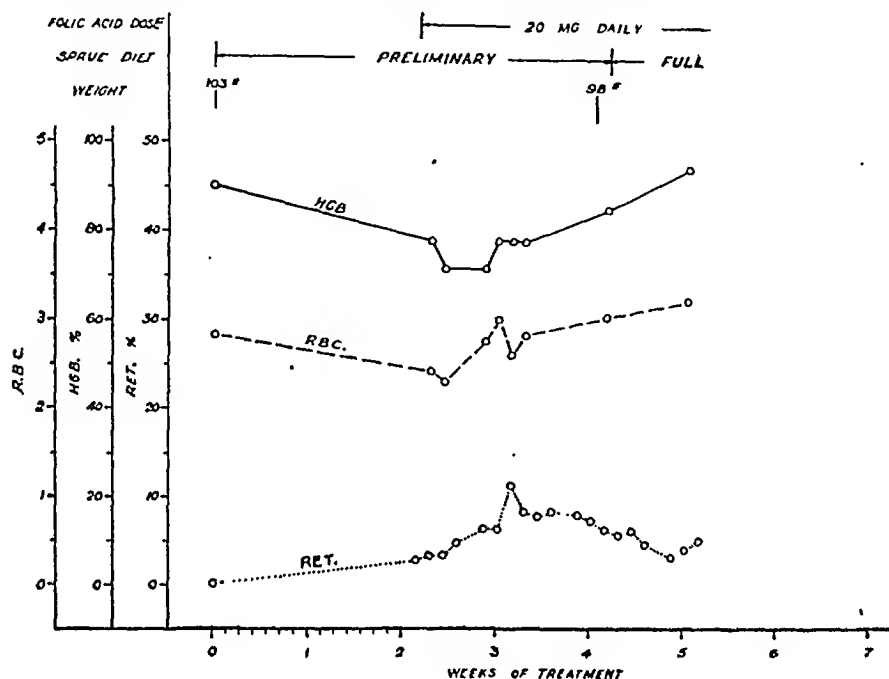


FIG. 15. Case 15.

to 40.4 per cent and the lymphocytic series had risen to 8.2 per cent. At the end of one month the patient had gained 10 pounds in weight and the gastrointestinal complaints, including glossitis, had entirely disappeared. The neurological signs and symptoms had not shown any trace of improvement.

This last case will serve to show how difficult it occasionally is to make a differential diagnosis between pernicious anemia and sprue in the presence of neurological signs and symptoms of combined system disease.

In favor of a diagnosis of pernicious anemia there were the macrocytic anemia, the megaloblastic bone marrow, the histamine-resistant achlorhydria and the neurological signs and symptoms of combined cord degeneration. In favor of sprue there were besides the above mentioned criteria, the loss of weight, the flat glucose tolerance curve, the high fat content in the stools, the suggestive "deficiency" pattern in the small intestine and the presence of pepsinogen and of a delayed renin reaction in the gastric secretion. Our question, which remains unanswered is: May not a patient with pernicious anemia in a tropical environment and under an inadequate diet develop those signs and symptoms which we have attributed to tropical sprue?

Of this series of 22 cases, 13 have been discharged and followed in the out-patient clinic. All these discharged patients have been receiving only 10 mg. of folic acid every seven days. So far none of them has shown any evidence of relapse, although three have been followed for nine weeks, and four additional cases for over a month. A few of them are at present in a better clinical and hematological condition than on discharge.

Twenty-eight old cases of sprue who had been under treatment in the out-patient department for one to 12 years were transferred to folic acid 10 mg. bi-weekly. Twenty-six of these patients had been receiving parenteral liver therapy (Lilly 343) 5 c.c. intramuscularly three times a week and two of them were getting brewer's yeast, 5 tablets (25 gr.), three times a day after meals.

It is interesting to state that in spite of prolonged liver therapy or of the administration of brewer's yeast, when the change in treatment was made only one of the 28 cases showed a red blood cell count of over 5,000,000 per cubic millimeter, seven cases had over 4,000,000 red blood cells and in 20 cases the red blood cell count was found to be less than 4,000,000 per cubic millimeter. All but four cases showed a macrocytosis of over 95 cubic microns and in several of them the mean cell volume was over 130 cubic microns. In three of the cases a megaloblastic bone marrow of 3.4 per cent, 3.4 per cent and 9.6 per cent, respectively, was observed. These figures show the tendency of the hematopoietic system of sprue patients not to exceed a certain level of response.

Nineteen of the 28 patients experienced a slight or moderate subjective and hematopoietic improvement, nine were in the same state after one and a half months of folic acid treatment. One patient who had troublesome diarrhea when folic acid was started, did so well and the stools became so hard with a dose of 20 mg. every other day that she omitted the drug for four days, when a new attack of diarrhea developed. At present we have been able to control the diarrhea again with a daily dose of 10 mg.

It has been generally accepted that sprue patients respond to parenteral crude liver preparations in which 1 c.c. is equivalent to 2 units, better than to the purified or concentrated extracts in which 1 c.c. contains 10 or 15 units. In 1938, we showed that in all cases except in those in which the initial red blood cell count was below 1,000,000, purified or concentrated liver extract was as effective as the diluted preparations in the treatment of sprue as judged by the hematopoietic response and the clinical improvement.

We have used Lilly's crude liver extract solution of 2 injectable U.S.P. units per c.c., which contains approximately 4.21 micrograms of folic acid per c.c., and Lederle's concentrated extract which contains approximately 6 to 7 micrograms per c.c. Of the former we have been using 6 c.c. daily intramuscularly which is equivalent to 25.26 micrograms of folic acid and of the latter 1 c.c. daily or 6 to 7 micrograms of folic acid. Undoubtedly liver extract must contain some other anti-anemic substance independent of and probably unrelated to folic acid.



## CONCLUSIONS

1. The efficacy of folic acid in the treatment of tropical sprue has been confirmed and extended.

2. We find that the daily oral administration of 10 mg. is adequate.

3. The administration of small daily doses is more effective than 50 times as much given in a single dose.

4. Observations made in five cases suggest that a daily dose of 20 mg. of folic acid together with an adequate sprue diet produces better results than the administration of larger doses accompanied by an inadequate diet.

5. Although we have not as yet definitely established the maintenance dose of folic acid, it is our impression that 2.5 to 5 mg. daily is an adequate maintenance dose for the majority of cases. This point is still under study. Certainly persons receiving a diet high in animal proteins and low in carbohydrates and fat would require a smaller amount than those receiving a diet low in animal proteins and high in carbohydrates and fats.

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# DIAGNOSIS OF OCCUPATIONAL DISEASE\*

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THE modern period of interest in occupational diseases had its inception following the epoch-making publication of Ramazzini in 1700.<sup>1</sup> In this comprehensive treatise were gathered the references of his predecessors on the subject of occupational disease. Ramazzini classified the diseases of nearly 100 different occupations in which hazards to health existed. The first essay on occupational diseases in the United States was written by McCready in 1835<sup>2</sup> and was recently published again.<sup>3</sup> Garrison<sup>4</sup> reviewed the literature on occupational diseases and spoke of "life as an occupational disease." In recent years there has been an increasing interest on the part of the medical profession in [the subject of] occupational disease by virtue of the introduction of Workmen's Compensation Laws making occupational disease compensable. The interpretation of what constitutes occupational disease and the methods of coverage vary in different states. Some state laws limit occupational disease to certain specific industries or to certain specific diseases that predominate in the industries of the state. Some state laws provide coverage by listing diseases and by schedule of conditions in which they are found in the industries.<sup>5</sup> This so-called schedule method of coverage has the great merit of certainty. It is informative to the employee as to the conditions under which he may make a claim, to the physician in attendance, and to the employer as to those conditions for which he may be held liable. This was the law of the State of New York for many years until 1935 when the compensation law was amended for the inclusion of "any and all" occupational diseases. The difficulty of a clearcut definition by law of what constitutes occupational disease has resulted in diverse medical problems. Occupational disease is most frequently defined as a disease "peculiar to" and "inherent in" a specific occupation, and one that is not usual in the general population.

A thorough and detailed history as to the present occupation and previous employment is essential in the evaluation of occupation as a possible cause of illness. The effects of occupational hazards have, to an increasing extent, been established through both clinical and experimental study. The U. S. Department of Labor<sup>6</sup> has listed 10 major hazards of employment. These are: (1) Abnormalities of air pressure, (2) abnormalities of temperature, (3) dampness, (4) defective illumination, (5) dust, (6) infection, (7) radiant energy, (8) repeated motion, pressure or shock, (9) poisons, (10) dermatoses. The most common of all occupational diseases is dermatosis. It has been estimated that the incidences of dermatoses among occupational

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diseases is 69 per cent. In order to establish proof of the occupational nature in the case of dermatoses, certain criteria are of distinct aid.<sup>8</sup> In attempting properly to evaluate the reporting of industrial dermatoses, Peck<sup>9</sup> has recently proposed that a special form be completed in each case.

It is recommended that in order to establish a diagnosis of occupational disease the following postulates be proved:<sup>10</sup>

- I. Exposure to a known harmful substance.
- II. The presence of clinical symptoms and objective findings resulting from contact with a specific harmful substance.
- III. Confirmation by established laboratory criteria.

#### I. EXPOSURE TO A KNOWN HARMFUL SUBSTANCE

The symptoms of occupational disease may be insidious in onset. Fumes, gases, vapors, dusts, metals and solvents, etc. may be classified as harmful substances. Experimental work on animals continues to be the basis of determining the allowable concentration of a hazardous substance and changes produced in tissues. Clinical experience, however, is the important guide in determining whether or not a hazard is injurious to the health of the worker. The symptoms of occupational disease frequently depend upon the character of exposure, the concentration of the noxious substances in the atmosphere and the mode of absorption. Poisoning by the absorption of lead is probably the best example of an occupational disease. The symptoms of lead poisoning may not arise for years in those exposed to the absorption of this heavy metal by way of the gastrointestinal tract. The inhalation of lead fumes or lead dust can and does produce symptoms of lead poisoning within several days or several weeks following absorption by way of the lungs. This can well be illustrated by the following experience.<sup>11</sup>

About 50 individuals developed signs and symptoms of acute lead poisoning following exposure to the inhalation of lead while employed as burners in the construction of a bridge. While driving hot rivets through the girders, red lead covering the girders was melted and lead fumes were created. The inhalation of these fumes caused symptoms of acute lead intoxication in the entire group within one to four weeks after such exposure. These individuals previously had worked as burners and iron workers for 10 to 15 years and had never been ill with any symptoms suggestive of lead poisoning. In this special job in the construction of one of the towers of a bridge, a situation had been created comparable to an enclosed chamber. All of the patients had gastrointestinal and neuromuscular symptoms commonly present in acute lead poisoning. Quantitative studies of a liter of urine revealed the presence of abnormal amounts of lead (more than 0.1 mg. of lead per liter). There were various morphological changes of the blood cells with an abnormal amount of stippling. The diagnosis of an occupational disease (acute lead poisoning) was relatively simple. The postulates of occupational disease as recommended, were proved. There was (1) a history of exposure to a known harmful substance, (2) the clinical symptoms and objective findings due to this harmful substance (lead) were present, and (3) there was confirmation by established laboratory criteria.

The differential diagnosis in occupational disease may at times present difficulties as can be illustrated by this case citation.

A white male adult, aged 58, had been employed for a period of three years in a cleaning and dyeing establishment. He was exposed to the absorption of various solvents, derivatives of both petroleum and benzene (benzol). The patient developed progressive weakness with increasing jaundice and on examination was found to have an enlargement of the liver. The patient was removed from his work, placed on a high carbohydrate, adequate protein and low fat diet. In addition, he received intravenous amino acid therapy and had large doses of vitamin B and liver concentrate intramuscularly. There was a period of temporary improvement following removal from his occupation and therapy which led to the impression that the patient's hepatitis was probably occupational in origin. After a period of several weeks, the jaundice became more intense and the liver became irregularly enlarged. At the time the patient was first seen, the results of laboratory investigations were inconclusive in differentiating between a parenchymatous and obstructive type of jaundice. At postmortem examination a carcinoma of the head of the pancreas was found.

The occurrence of jaundice in a patient who is working with carbon tetrachloride for example may be an expression of a hepatitis due to the absorption of this chlorinated hydrocarbon. However, in the differential diagnosis, obstructive lesions in the biliary tract should always receive consideration even though an individual may be working with a substance which is known to be toxic to the liver. There are many individuals whose occupation brings them in contact with what is usually recognized as a harmful substance, yet never develop signs or symptoms of occupational disease.

Proper ventilation, proper exhaust system, proper wash-room facilities and all other adjuncts of an adequate program of industrial hygiene will prevent absorption of toxic substances and illness. Diagnosis of an occupational disease may be suspected or made more readily when the chemicals or materials with which the individual is working are known. Exposure to the concentration of vapors which can be considered abnormal will produce illness as illustrated by the following illustrative cases.

Some three years ago, about one dozen men were examined who became ill as a result of their occupation of rubberizing cloth. Various solvents were used including ethyl ketone, toluol, gasoline and ethylene dichloride. During the years prior to the war, there had been no illness among these men. With the speeding up of activities, the concentration of these materials in rubberizing balloon cloth was increased, with the result that illness especially related to the gastrointestinal tract developed among these workers. With the introduction of adequate ventilation and exhaust systems and the use of certain chemical substitutes, the complaints ceased.

Although the maximum permissible concentrations are helpful guides in the diagnosis, as Greenburg and Moskowitz<sup>12</sup> point out, they are not complete substitutes for the periodic medical examination of the workers. The lack of health education among employer and employee groups and the importance of stressing the possible effects of contact with harmful substances can best be illustrated by the following incident:

About three years ago, half a dozen patients were examined who had developed methyl bromide poisoning while engaged in filling glass ampules with the solution. One of the patients died as a result of severe central nervous system involvement. Neither employer nor employees had been instructed as to the proper safeguards necessary in the filling of these glass ampules to prevent the toxic effects of methyl bromide which readily vaporizes and may produce irreversible changes in the central nervous system.

## II. THE PRESENCE OF CLINICAL SYMPTOMS AND OBJECTIVE FINDINGS RESULTING FROM CONTACT WITH A SPECIFIC HARMFUL SUBSTANCE

By virtue of accumulated medical experience and numerous reports in the literature, a physician today is cognizant of the clinical symptoms and objective findings that are usually associated with occupational disease. The terms "peculiar to" and "characteristic of" employment, as commonly used in defining occupational disease, are based on the fact that in many instances of occupational disease there are distinctive clinical symptoms and objective findings. As an illustration of clinical symptoms and findings in an occupational disease, the following illustrative case of benzol poisoning may be cited.<sup>13</sup>

A male, white adult, 43 years of age, had worked as a pressman on black and white presses for a period of 25 years. During this time, he was always well. Following the installation of multi-colored presses, benzene (benzol) was used as a solvent for a variety of colored inks and some three to four months later the patient developed progressive weakness with purpuric manifestations under the skin and bleeding from the nose, gums and gastrointestinal tract. Blood studies revealed the presence of a pronounced anemia, leukopenia and thrombocytopenia. At postmortem examination a complete aplasia of the bone marrow was present. Investigation had revealed that the patient was exposed to the inhalation of benzene (benzol) vapors which ranged from 50 to 740 p.p.m. of air.

Solvents are used on a large scale in industry because they are avid for fats and are volatile. They belong either to the coal tar (aromatic or benzene) series or to the petroleum (aliphatic or fatty) series. Absorption takes place either through the lungs or skin. The absorption of solvents through the stomach is only of minor, practical significance.<sup>14</sup> Solvents are, for the most part, eliminated through the lungs depending upon their volatility or solubility. Some are eliminated by the kidneys and others through the skin, intestines and liver. The liver forms the chief store-house for many of the solvents, which explains the severe injuries to this organ. Gastrointestinal symptoms followed by hepatitis may characterize the absorption of the chlorinated hydrocarbons, as illustrated by the following case citation.

Two patients, both alcoholics, developed hepatitis following the absorption of carbon tetrachloride and, in one instance, evidence of renal complications became manifest. The postmortem examination and histologic study showed in both instances

evidence of acute necrosis of the liver, and in the second instance there was associated toxic nephrosis.

Exposure to chlorinated naphthalenes and diphenyls is known commonly to produce typical acneiform eruptions, and occasionally absorption may cause serious liver damage as may be illustrated by the following case report:

A white, male, adult, 42 years of age, was exposed to the inhalation and absorption of hot "Halowax," and developed an acneiform eruption some two months after first contact with this solvent. Nausea, occasional vomiting and jaundice became manifest after several months' absorption of this chlorinated hydrocarbon. There was progressive increase in the size of the liver with increase of the icterus index. The patient was removed from his occupational contact and admitted to the hospital. He failed to respond to all types of therapy. There was progressive diminution in the size of the liver and fall of the blood protein level. The patient died eight months after his first occupational contact with the solvent. At autopsy, there was distinct diminution in the size of the liver, general irregularity and hob-nailed appearance. The findings were those of acute atrophy.

The clinical symptoms and objective findings that are usually present with absorption of metals have been described on many occasions in the past and the diagnosis is, as a rule, not difficult. Poisoning by lead, arsenic, mercury, cadmium, etc. usually presents a clinical picture with which the physician is familiar. Occasionally, however, the differential diagnosis between occupational and non-occupational disease may present difficulties, as illustrated by the following case citation:

A white male adult, 40 years of age, had been exposed to the absorption of lead while employed as a garage worker for a period of 10 years, when he developed unilateral convulsive seizures affecting the right upper and lower extremity. Examination of the spinal fluid and ocular fundi revealed normal findings. Pneumo-encephalogram revealed no abnormalities. Although a brain tumor was suspected, a diagnosis of chronic lead absorption with abnormal neurological manifestations was made on the basis of occupational exposure to the absorption of lead and the findings of an increased amount of lead in the urine and whole blood. The absorption of this heavy metal does not necessarily imply that atypical and bizarre clinical symptoms are necessarily due to such absorption. The patient was operated upon and a brain tumor removed. Recovery was uncomplicated. There were no further convulsive seizures.

Although lead may affect the nervous system, it does not necessarily follow that neurological symptoms that cannot be explained on any other basis are necessarily due to the occupational hazard. The physician recognizes the fact that the vast majority of illnesses that occur among workers are non-occupational in origin. Patients with abdominal colic due to lead poisoning have been erroneously operated on for acute appendicitis. The contrary is also true. There are instances where a patient is treated for lead colic when acute appendicitis is present. A detailed and thorough occupational history is necessary as an aid in the differential diagnosis. All physicians, especially the industrial physician, should be familiar with the hazards of all materials used in a specific industry.

## III. CONFIRMATION BY ESTABLISHED LABORATORY CRITERIA

In many instances where occupational disease is suspected, laboratory aids are of importance in establishing a diagnosis. The laboratory investigations that can be of value are:

1. Studies of the working environment, dust sampling, air analysis, etc.
2. Examination of biological materials.
3. Blood chemistry studies, blood count, etc.
4. Roentgen examination.

The presence of an abnormal concentration of gases, dusts, metals, etc. in the atmosphere can be considered as proof of working conditions that are harmful. Examinations of biological materials on a quantitative basis for metals such as arsenic, mercury or lead are of value in the differential diagnosis. The presence of abnormal amounts of heavy metals such as lead in the urine is an index of an abnormal degree of absorption. The presence of an abnormal amount of stippling of the red blood cells may also be used as an index of abnormal absorption of this heavy metal. Even though clinical symptoms of intoxication may not be present, these examinations may be used as a basis for the evaluation of the degree of absorption. In the presence of gastrointestinal symptoms that possibly can be attributed to the various solvents, the icterus index may be increased even before there is evidence of liver enlargement or even before jaundice can be detected. Roentgenograms of the lungs should be made routinely in all individuals who are exposed to the inhalation of asbestos or to the inhalation of silica. There is a large amount of literature on the subject of silicosis. It is well recognized that the inhalation of this inorganic dust over a period of years is necessary before there is roentgen evidence of discrete, bilateral, symmetrical nodulations which may be associated with conglomeration of these nodules and complicated by infection. The term pneumoconiosis has been used to designate all forms of pulmonary reaction to inhaled dust, with no implication as to the character, severity or effect on function. Many of the dusts which are inhaled are neither toxic, allergenic nor pathogenic. They produce no symptoms, no disability and no predisposition to tuberculosis, and, as expressed by Gardner,<sup>15</sup> "they are known largely for their shadows cast on a roentgenogram." Since benign pneumoconiosis produces nothing but shadows cast on a roentgenogram and without any concomitant or subsequent pulmonary or cardiac complications, Pendergrass and Leopold<sup>16</sup> have stated "it is unfair to the worker, to labor and to industry for the clinician and roentgenologist to take their responsibility lightly when called upon to differentiate between silicosis and asbestosis on the one hand and benign pneumoconiosis on the other. The differentiation must be obtained by detailed occupational history, knowledge of the environmental conditions serving the worker, and an industrial engineering survey to determine the nature and concentration of the dust to which the employee is exposed. The



importance of this statement is stressed, for, in the differential diagnosis of silicosis, such conditions as miliary tuberculosis, pulmonary manifestations of sarcoidosis<sup>17</sup> and of mitral stenosis<sup>18</sup> and other forms of pneumoconiosis must be considered. A correct diagnosis is essential not only from the point of view of compensation benefits but more especially from the therapeutic point of view, for the use of metallic aluminum or amorphous hydrated alumina is indicated if the patient has silicosis or is exposed to the inhalation of silica. In any suspected case of occupational disease, laboratory investigations should be done at an early date, for following removal from work, the patient's symptoms may improve and laboratory studies be of little value.

*Occupational Accidents.* Poisoning by carbon monoxide, sulfur dioxide, by other gases and fumes and by septic infection is classified in the State of New York<sup>19</sup> as "occupational injuries due to harmful substances." Acute poisoning is usually the result of an accident and such poisoning should not be classified as an occupational disease. Infection as a result of possible contact due to occupation should be classified as an occupational accident and not as an occupational disease. A nurse, prior to employment in a hospital for the tuberculous is found to be well after physical examination, roentgenogram of the chest and tuberculin skin testing. Subsequently, the nurse may develop pulmonary tuberculosis. It is well recognized that pulmonary tuberculosis exists among the general population entirely irrespective of occupational activity. While the nurse may have had contact with some active case of pulmonary tuberculosis away from her work, the occupational contact as a factor responsible for the onset of her illness cannot be denied. The rare incidence of anthrax in an individual who is a wool-sorter does not necessarily mean that the occurrence of the malignant pustule is due to the occupation, especially where it can be shown that the patient may frequently be shaved by a barber. Anthrax may have been caused by the entry of the germ from the use of the barber's brush. Tularemia may occasionally occur in a butcher who has skinned an infected rabbit and accidentally cuts himself. It is evident that infection as a cause of illness should not be classified in the category of occupational disease but rather as an occupational accident.

Occupational factors may be responsible for the onset of an attack of asthma, but this illness itself cannot be classified as an occupational disease. It has been shown that about 10 per cent of the population have an underlying constitutional predisposition to manifestations of allergy.<sup>20</sup> Individuals who have this familial or hereditary predisposition to allergic phenomena may develop clinical symptoms of asthma as a result of exposure to certain specific allergens in their work.<sup>21</sup> Following removal from the occupation, the individual may recover from his attack. In some, however, especially where asthma develops in middle life due to a specific allergen of occupational origin, subsequent infection may arise and a chronic bronchitis develop. The patient may become sensitized to the bacteria responsible for the bronchitis and a chronic form of asthma of bacterial origin may develop.

The difficulty in classification of occupational diseases becomes manifest when one attempts to classify such illnesses as frost-bite. As a result of exposure to cold and dampness over a prolonged period of time, disease of the peripheral vascular system with the clinical phenomena of frost-bite may occur. Frost-bite should not be classified as an occupational disease although it may possibly be classified as an occupational accident even though there is nothing accidental in an occupation that causes continuous or frequent exposure to any continued low temperature during the winter months.

The teaching of industrial medicine, a broad term which includes such subjects as occupational disease, industrial hygiene, health education in industry, etc., is slowly finding its way into the curriculum of the medical student. Physicians are becoming increasingly aware of the importance of the hazards of occupation as they may exist where there is exposure to the absorption of dusts, fumes, solvents, noxious gases, metals and other injurious substances. Methods for control of occupational disease have been developed by health authorities. A program of health education is important both to the employer and employee groups.

Absorption of the solvents is frequently manifested by early gastrointestinal disorders.<sup>22</sup> Nasal symptoms or slight cough are frequently among the early symptoms of impending asthma.<sup>21</sup> Medical guidance is of importance in order to prevent structural damage and progressive disease. The medical aspect of occupational disease has as its primary objective the prevention of occupational disease. Adequate and proper laboratory facilities should be available in all communities so that the general practitioner can have early aid in his diagnostic problems where occupational disease is suspected. There are problems related to the diagnosis of diseases due to occupational factors that require research and investigation. In this industrial age the question arises, what is the normal content of metals in biological materials? What is the normal content of metals in viscera when analyzed after postmortem examination? Some work has been done in this field but there are many questions relating to these and other problems that are yet to be answered. We are living in an industrial age and many individuals who have no specific occupational contact with such metals as cadmium, lead, arsenic, etc. absorb and deposit in their tissues certain quantities of metals. With a program of undergraduate and postgraduate instruction, with adequate laboratory facilities available and with expanding programs on industrial health, early diagnosis and treatment of diseases of occupation and more especially prevention of occupational disease, may be anticipated.

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# IMMOBILIZATION OF BOTH LUNGS PRODUCED BY THE EQUALIZING PRESSURE CHAMBER WITH RESULTS OF TREATMENT IN PULMONARY TUBERCULOSIS \*

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THE purpose of this communication is: (1) to present the mechanism by which both lungs are immobilized with a normal exchange of oxygen and carbon dioxide between the pulmonary alveoli and the outside air; (2) to report the results of nine years' trial of local lung rest therapy in advanced and moderately advanced pulmonary tuberculosis.

When absence of breathing is produced by hyperventilation with 100 per cent oxygen, the subject remains comfortable, has no impulse to breathe, and his chest remains motionless for a period of five minutes. Since the provision of an adequate arterial oxygen tension is sufficient to prevent normal breathing when carbon dioxide has been eliminated by increased ventilation, it is evident that chemical factors in respiration may take precedence over proprioceptive reflexes from the moving frame-work of the lungs and chest wall.

In 1926 Thunberg<sup>1</sup> developed a "barospirator" in which patients were completely enclosed within a steel chamber and exposed to an alternating pressure of one-sixth of an atmosphere 25 times a minute. The apparatus was employed as a method of artificial respiration in cases of respiratory paralysis due to poliomyelitis and morphine poisoning. Although this alternating pressure results in a flow of approximately 500 c.c. of air in and out of the lungs, studies carried out in our laboratory indicated that a normal arterial oxygen and carbon dioxide pressure was not maintained in experimental respiratory paralysis.<sup>2</sup> The resistance of the tracheobronchial passageway was found to account for the observed fact that an initially higher pressure was applied to the chest wall during the positive phase than to its inner surface and, conversely, that an increased negative pressure was initially exerted on the outer thorax and abdomen during the phase of negative pressure as compared to that which arrived within the lungs.

In order to equalize the pressure on both sides of the chest wall, as well as the upper and lower surface of the diaphragm, the alternating pressure wave had to be delayed from striking the chest wall until it had arrived

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within the lungs and the resistance of the tracheo-bronchial tree compensated for by diminishing the pressure exerted on the outer chest wall by approximately 5 cm. This was accomplished by separating the body compartment of the chamber from the head end by a movable appropriate partition, resembling a collar about the neck. Air under pressure first passes into the head compartment, enters the nose and tracheo-bronchial passageway as the pressure wave continues to the body end of the chamber through the constricted opening about the neck, exerting a pressure on the chest wall approximately 5 cm. less than that present in the head end of the chamber. In this way an equal pressure was simultaneously applied to the inner and outer surfaces of the chest wall as well as the upper and lower surfaces of the diaphragm.

In animals subjected to respiratory paralysis, a normal tension of oxygen and carbon dioxide in the arterial blood was maintained with the equalizing pressure device, whereas asphyxia took place with alternating pressure alone. In human subjects a slight initial compression of the chest was observed during the positive phase of alternating pressure with a corresponding expansion during the negative cycle of alternating pressure. In patients the degree of movement of the chest wall was seen to depend on the resistance in the tracheo-bronchial tree. In those with pulmonary emphysema and asthma a marked bellows-like expansion and contraction of the chest wall was manifested during the negative and positive cycles of pressure, respectively. In patients with pulmonary tuberculosis in whom fibrosis and emphysema were present immobilization of the lung could not be obtained, because the pressure wave could not be sufficiently delayed by the mechanism described above. In most patients, however, a decrease of 5 cm. of pressure in the pressure that arrives in the body compartment, as compared with the pressure present in the head end of the chamber, was sufficient to accomplish mobilization of the lung and cessation of voluntary respiration. Ability to dispense with the habit impulse to breathe requires a variety of training of from two to three hours to two to three days. The oxygen saturation and  $\text{CO}_2$  content were found to be normal in patients who learned to suspend voluntary respiration.

Several methods were employed to teach the patient to renounce the habit of breathing. The simplest procedure was to instruct him to take a breath at the start of the positive cycle; the onset of positive pressure revealed to the patient by observing a ribbon suspended at the head end of the chamber, which is thrown upwards with the inrush of air. Another method used was to say "In" through the speaking tube when the gasometer indicates the shift of pressure to the positive side. After five or six shallow inspirations the patient is instructed to allow the air to enter his lungs without conscious effort. During the first hour or two, or the first several days, a recurrent impulse to breathe manifests itself, but as the treatment is continued patients learn to lie in the chamber for hours at a time without breathing. Coughing or talking results in momentary chest movement.

The effect on the ear drum of the oscillating pressure is similar to swift descent and ascent from high altitude. At first this is found uncomfortable, but in all instances the patient has become largely oblivious of the sensation. A sponge rubber covering over the ears or a radio microphone has been employed to minimize this sensation. Congestion in the sinuses and in some instances pain may take place as a result of the oscillating pressure but this discomfort is generally temporary and has not prevented the employment of the chamber in any case. Spraying the nose with a vasoconstricting solution, such as neosynephrin and privine, has been found helpful. In certain cases the treatment has been interrupted for one or two days and then recommenced.

The effect of cessation of breathing on the central nervous system is of considerable interest. The impulse for movement of the voluntary muscles in the extremities is strikingly diminished. The patient may lie in the chamber for hours without moving his hands or changing position. The desire to smoke disappears when voluntary respiration stops even in patients who have been accustomed to smoking two packages of cigarettes daily. In many instances the relaxation is of such a nature that the patient does not require amusement although in other cases a radio has been employed for that purpose.

Roentgenograms of the chest taken during the positive and negative phase of pressure on the same film, during residence in the equalizing pressure chamber, revealed no movement of the ribs or diaphragm.<sup>2</sup> It seemed to us that a tentative hypothesis could be formulated that this type of local lung rest, in which movement of the lungs either does not take place, or if it goes occur, is of minimal degree compared to the known excursions of voluntary breathing, would favor the process of healing by reducing changes in the physical state of the tuberculous lesions and that absence of lung movement might have a specific effect in collapsing those cavities in which a check-valve mechanism had been previously operating to keep the cavity inflated. During normal breathing inspiration is followed by enlargement of the cavity, with inflow of air into it; during expiration a variable delay in the exit of air from the cavity may take place, depending upon the narrowing of the bronchus leading to it, at times with some increase in distending pressure on the inner wall of the cavity. This sequence of events may be prevented by residence in the equalizing pressure chamber. The cavity does not undergo, in all probability, expansion and contraction that occur with normal breathing. If the bronchus to the cavity is closed off, or exceedingly small in relation to the total volume of the cavity, some contraction and expansion of air within the cavity will take place. Since one of the most striking effects of arrested lung movement has been the disappearance of cavity, the likelihood that cavity closure takes place as a result of removal of the check-valve mechanism of normal inspiration and expiration gains support.<sup>4</sup>

In earlier publications it was shown that a course of five hours daily for a period of two to three months is inadequate to accomplish therapeutic results.<sup>3, 4, 5, 6, 7, 8, 9</sup> Patients have been treated from eight to 11 hours daily for a course arbitrarily set at three and one-half to four months. When marked clinical improvement has been initiated the patient is allowed freedom from the chamber for a variable period of bed rest or convalescent care. Of the 12 patients who have been treated by residence in the equalizing pressure chamber one has had three courses of treatment, three have had two courses, and the remainder (eight cases) one course.

The follow-up results of cases previously described will be presented. In the accompanying table (table 1) the results of treatment have been

TABLE I

Results of Immobilization of Both Lungs by Residence in the Equalizing Pressure Chamber in Advanced Bilateral and Moderately Advanced Pulmonary Tuberculosis

Case No.	Diagnosis	Number of Courses	Results	Remarks
1	Chronic pulmonary tuberculosis; bilateral, advanced laryngeal tuberculosis	1	Clinical recovery	Had had negative sputa for 7 years and been at work 6 years except for 3 months bed rest
2	Chronic pulmonary tuberculosis, bilateral, advanced	1	Clinical recovery	Negative sputa and at work one year when follow up ended
3	Chronic pulmonary tuberculosis, unilateral, moderately advanced	1	Apparent clinical recovery	Recent case with negative sputa and apparent arrest but follow up only 3 months
4	Chronic pulmonary tuberculosis, bilateral, moderately advanced	2	Clinical recovery	Negative sputa; at work for follow-up period of one year
5	Chronic pulmonary tuberculosis, bilateral, advanced	2	Clinical recovery	Negative sputa 5 years; arrest of disease, at work 4 years
6	Chronic pulmonary tuberculosis, bilateral, advanced	3	Clinical recovery	Negative sputa and at work 4 years. Cavity closed on each of 3 courses
7	Chronic pulmonary tuberculosis, bilateral, advanced	2	Marked improvement	Negative sputa past 4 years; at work intermittently; apparent recurrence of small cavity
8	Chronic pulmonary tuberculosis, bilateral, advanced	1	Slight improvement, lost when treatment ended	The first case, treated 6 hours a day for 2 months only
9	Chronic pulmonary tuberculosis, bilateral, advanced	1	Moderate improvement, lost when treatment ended	Large cavity on left closed but re-expanded on slight activity
10	Chronic pulmonary tuberculosis, bilateral, advanced	1	Moderate improvement, lost later	Patient began treatment with T. 104 F. Treated 2 months, transferred for 3 weeks to oxygen chamber, died 3 months later
11	Chronic pulmonary tuberculosis, bilateral, advanced	1	No improvement	Thoracoplasty on one side later. Condition fair
12	Chronic pulmonary tuberculosis, bilateral, advanced	1	No improvement	No collapse. Cavities apparently adherent to chest wall

summarized. Our main emphasis in this paper will be to indicate the specific effect of immobilization of the lungs on cavity closure in cases that have had repeated courses of treatment.

As will be seen in table 1, there were two cases in which a clinical recovery followed a single course of treatment, and an additional third case,

recently treated, that is apparently obtaining an arrest of his disease, as indicated by negative sputum tests and clearing of infiltrative lesions in the lungs. Of three cases treated with two courses two became clinically well; the third case showed conspicuous and marked improvement, with concentrate sputum and gastric tests repeatedly negative in the past four years. However, roentgenograms reveal a highlight area that suggests a small cavity at the site of his original large cavity. Intermittently at work for three years, he is now in a municipal tuberculosis hospital.

The clinical course of the patient who had three courses of treatment (Case 6) will be presented. His first history appears as Case 2 in a previous publication.<sup>4</sup>

This patient was a man 31 years old at the time of his original admission to Presbyterian Hospital. He had had clinical symptoms of pulmonary tuberculosis for nine months prior to admission to a municipal hospital where he ran a fever of 100 to 101° F. for two months at bed rest. Roentgenograms of the chest showed an oval cavity at the level of the right second interspace measuring 2.5 cm. in a vertical direction and 1.5 cm. transversely. On the left side a cavity was present near the anterior chest wall at the level of the third rib which measured 2 cm. in diameter and beneath it another cavity measuring 1.2 by 1.7 cm. The upper half of both lungs beneath the cavity showed dense infiltration.

After three months of residence in the equalizing pressure chamber, about 10 hours daily, the cavity on the right side had disappeared and one of the cavities on the left side was not visualized on roentgen studies. The patient gained 17 lbs., the sedimentation rate and temperature became normal. The patient was then discharged from the hospital and put on a convalescent bed rest program at a sanatorium. The lesions on both sides continued to clear and coalescence of the cavities in the left lung formed a single cavity 2.4 by 3 cm. seven months after discharge (13 months after onset of first treatment). As seen in the roentgenograms (figure 1), the cavity on the right had disappeared and the dense infiltration on both sides had strikingly diminished between the onset of the first course and the beginning of the second course of therapy.

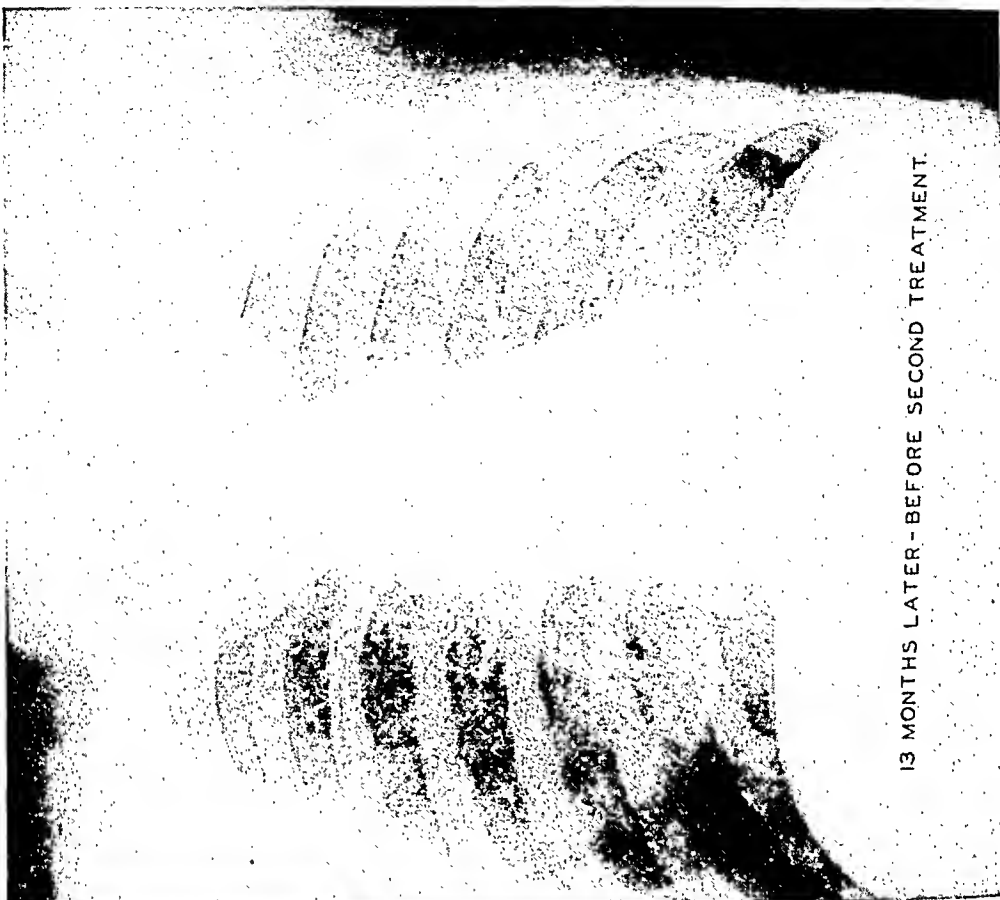
The second course of three months' treatment resulted in apparent closure of the large cavity on the left side, as seen in figure 2. A small shadow of approximately 0.6 cm. in diameter appeared to represent a possible cavity remnant. The patient then left the hospital and led a life of irresponsible, varied activity for one year, when he was again admitted for additional treatment. The cavity in the left lung field had again increased in size to 3.5 by 2.5 cm. A course of five hours a day, with the patient ambulatory the rest of the time, was experimentally tried but the cavity was only slightly diminished in size. A subsequent course of 10 hours a day was then followed by disappearance of the cavity as well as clinical evidence of recovery. The roentgen reproduction of figure 3 illustrates the closure of this relatively large and thick-walled cavity. The patient was at work for the following four years with consistently negative sputa tests, and repeated roentgenograms revealed no evidence of recurrence.

The sequence of events in this case indicates the specific effect of lung immobilization, as may be seen by the following summary: (1) Disappearance of the cavity in the right lung and decrease in size of cavity in left lung after the first course; (2) increase in size of cavity in left lung after six months modified bed rest; (3) collapse of cavity in left lung after second





BEFORE FIRST COURSE OF TREATMENT



13 MONTHS LATER - BEFORE SECOND TREATMENT

FIG. 1. Clearing of infiltration and cavity in the right lung between the onset of first and before the second course of treatment. Case 6.

course; (4) reexpansion of cavity in left lung after one year's activity; (5) closure of cavity after third course, followed by clinical recovery and ability to work for four years.

The case history of Case 7 in table 1 (previously described as Case 4 in the earlier publication<sup>4</sup>) also reveals the effect of immobilization of both lungs in closure of a cavity of large size. This patient was a man 44 years of age. One year before admission to Presbyterian Hospital he experienced onset of cough with several large

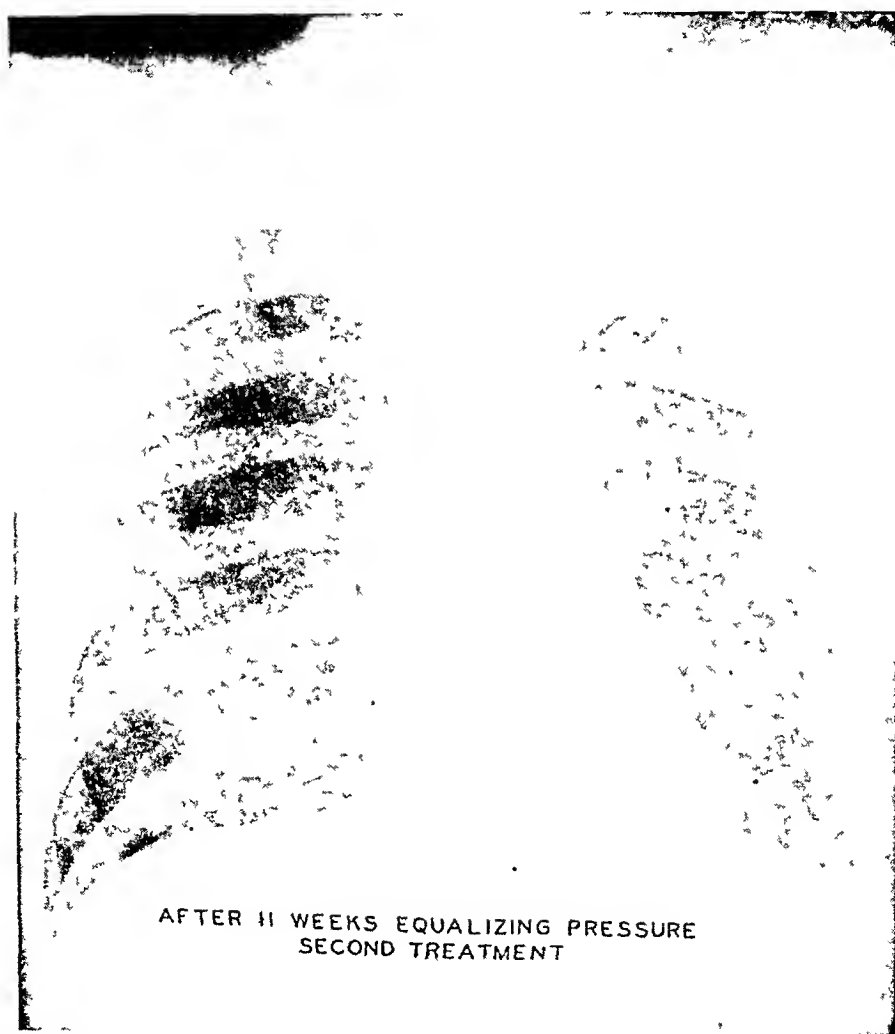


FIG. 2. Closure of cavity in left lung after eleven weeks of second course Case 6

hemoptyses, gradual weight loss, weakness and night sweats. He entered a city hospital where pneumothorax was tried and abandoned.

After rest in bed for 5½ months the temperature of the patient fell from 102 to 99° F. and he gained 30 lbs. There was some decrease in the size of a cavity which on roentgen examination measured 3 by 4 cm. at the level of the left first interspace. There was a dense exudative and productive infiltration on the left side and a scattered bronchogenic spread in the base. Between the time of his transfer from the city hospital to the Presbyterian Hospital the cavity increased in size, extending,

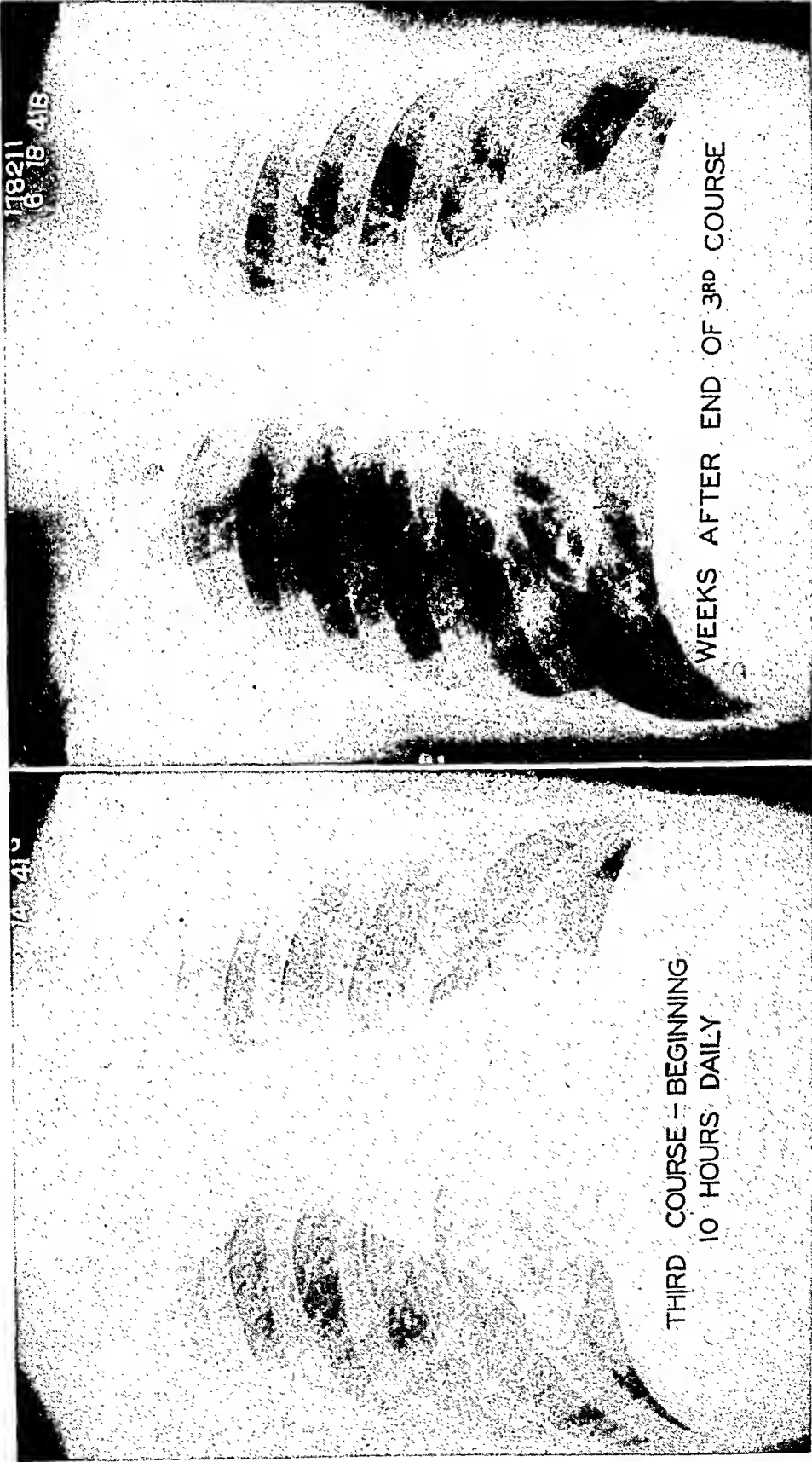


FIG. 3. Closure of cavity in left lung after third course. Case 6.

according to planigrams, from the fourth to the twelfth centimeter levels, as measured from the roentgen table, the patient lying on his back. At the end of four months residence in equalizing pressure chamber the sputum became negative for tubercle bacilli and roentgen examination showed a marked decrease in the infiltration in the left lung field, and an apparent disappearance of the cavity on both planigraphic and stereoscopic roentgenograms. The upper portion of the accompanying photograph (figure 4) reveals the roentgen appearance of the lungs before the first course of treatment and after four months of equalizing pressure therapy.

On his return to the city hospital an initial sputum was positive but five later examinations of concentrated sputum were consistently negative. However, the cavity became definitely visible on subsequent roentgenograms and, five months later, the patient returned to the Presbyterian Hospital. During the five month period when he was at the city hospital, his weight had decreased from 158 to 146 pounds. The sedimentation rate was 20 mm. after the first course and on readmission was 77 mm. Stereoscopic films of the chest which had shown a collapse and virtual disappearance of the large cavity in the left upper lobe after the first course revealed on readmission a large excavation, 5.3 cm. in diameter, containing a small amount of fluid, surrounded by a zone of infiltration 8 mm. in thickness in its outer portion and somewhat more in its inner portion. The amount of infiltration in the lung below the cavity had increased considerably, as compared with the film made at the end of his last admission.

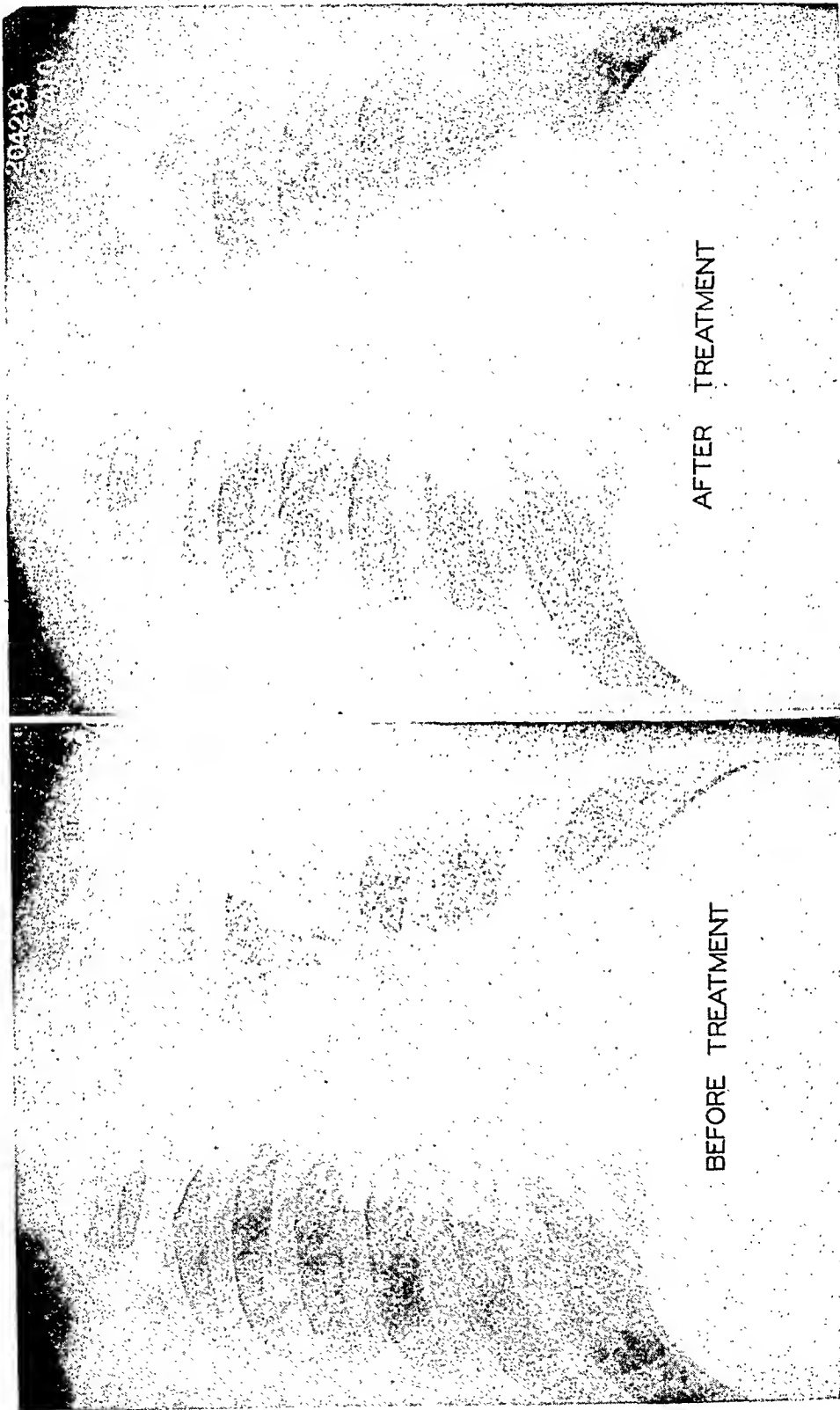
During the second course his weight increased to 181 pounds. The sedimentation rate decreased to 8 mm. in one hour. The sputum became consistently negative and during the last three months expectoration almost disappeared. The lower portion of figure 4 shows the disappearance again of the cavity in the left upper lobe and the decrease in the surrounding infiltration. The planigraphic roentgenograms (figures 5 and 6) demonstrate the closure of the cavity after the first and second courses. An apparent fibrous scar replaced the cavity after the second course. There was marked clearing of the infiltration below the cavity.

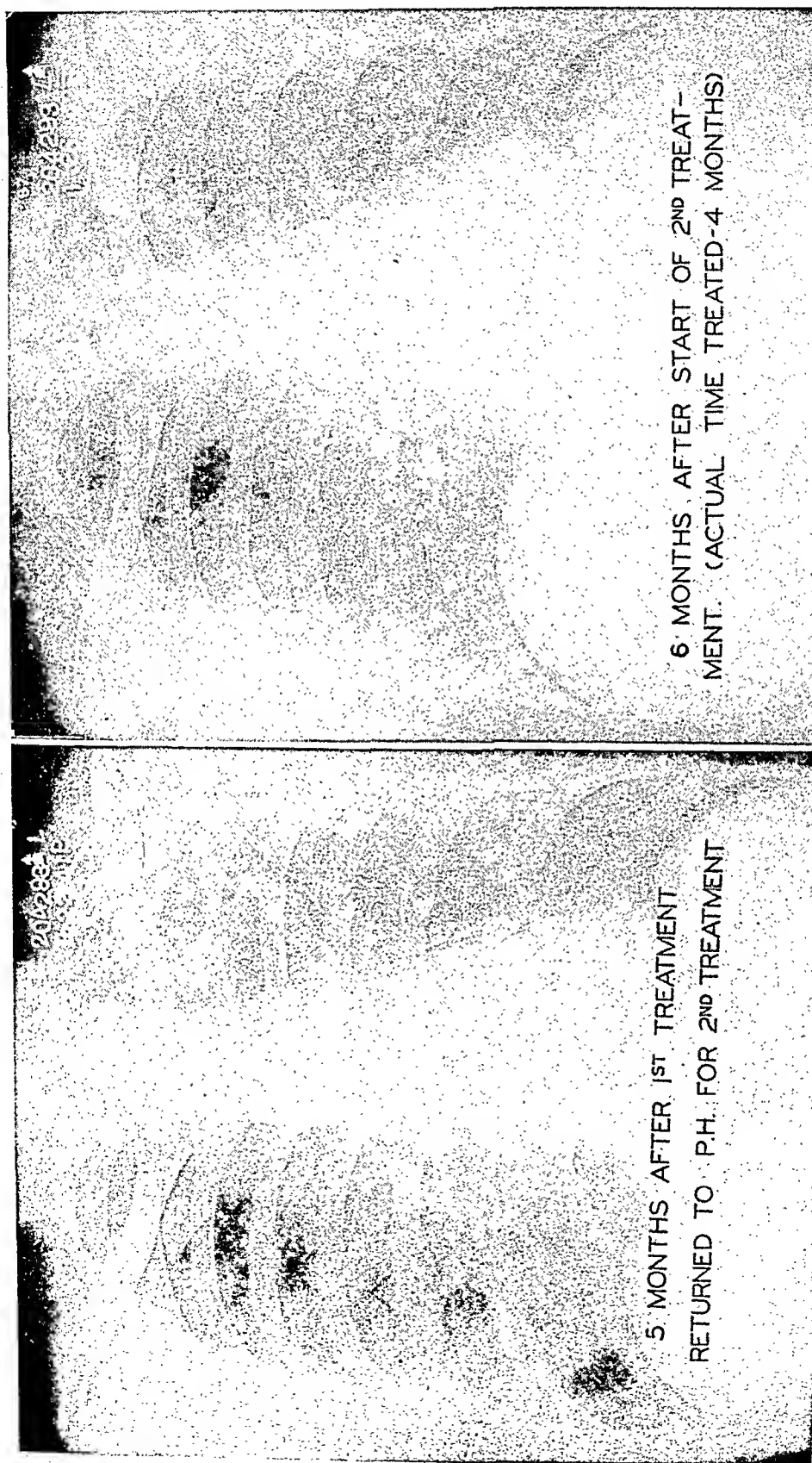
During one period of two weeks the patient resided in the equalizing pressure chamber for 20 hours a day. At the end of this time he developed pain and some discharge in both ears. No sponge-rubber covering for the ears was used at that time. Roentgen examination of the mastoids was negative. Examination of the ears was essentially negative although some impairment of hearing was present. The patient was transferred to a municipal hospital for convalescent care.

Examination of the sputum and gastric lavage specimens has continued to be negative for four years and he has been at work intermittently. At present an apparent cavity of 1 cm. in diameter is indicated by roentgen examination.

In this patient the collapse of the cavity and the substantial clearing of infiltration below the cavity were clearly observed as a result of the first course of treatment. The subsequent re-opening and enlargement of the cavity when the patient was at bed rest and the final closure of this cavity after the second course of treatment cannot be easily explained except as a specific effect of cessation of lung movement.

In re-appraising the results of two patients in whom no diminution in the size of the cavity took place the factors considered were (1) the possibility that the cavities were adherent to the chest wall over a wide area and (2) that continuous arrest of lung movement was not obtained because of failure of adequate supervision. It was observed that one of these patients frequently fell asleep and that during sleep breathing took place.





4b

FIG. 4. Closure of cavity and decrease of infiltration after first and second courses. Case 7.

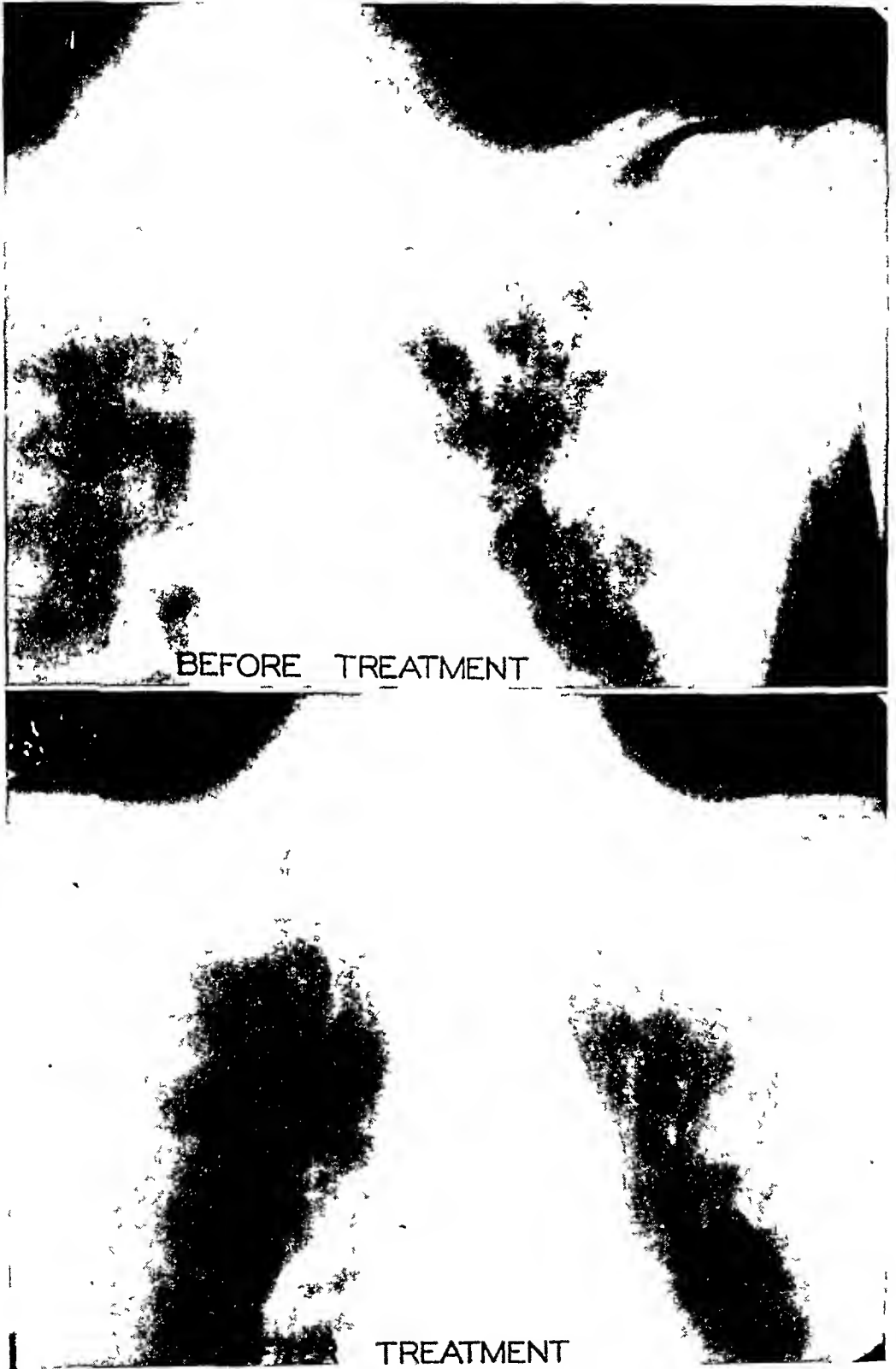


FIG. 5. Planigraphic roentgen-ray showing disappearance of cavity after the first course.  
Case 7.

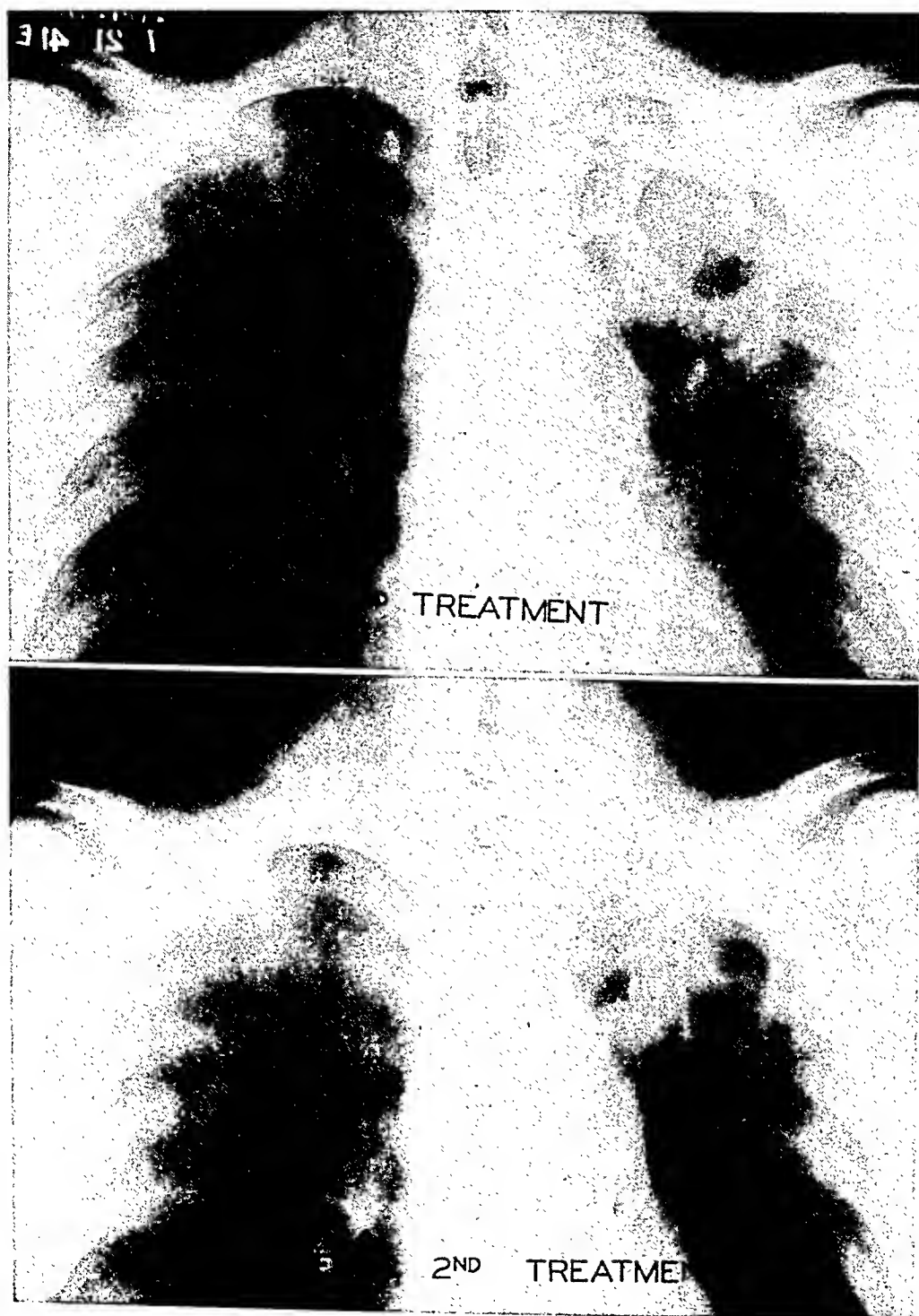


FIG. 6. Planigraphic roentgen-ray showing disappearance of cavity after the second course.  
Case 7.



The mechanism of improvement does appear to be related to the cessation of lung movement, which not only diminishes the diffusion of toxins from the tuberculous lesions but provides in most cases an unusual form of mental and body rest. The removal of the check-valve mechanism in cavity inflation would seem to be involved in the closure of cavities that has been described above. Studies of the method of immobilizing lung therapy have continued during the past nine years. The technic of regulating the alternating and equalizing pressures has become simpler and better understood.

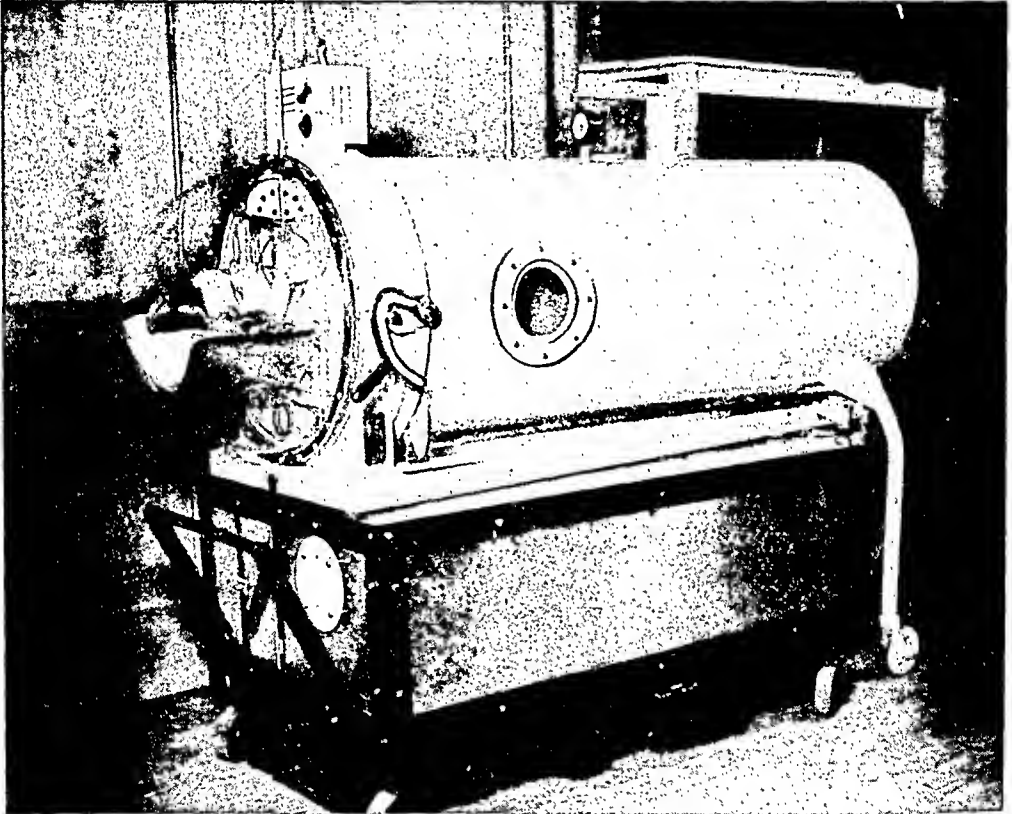


FIG. 7. Equalizing pressure chamber.

The results obtained have been sufficiently favorable in some patients for whom no other program of therapy was possible, and in whom other measures had been tried and found ineffective, that we have concluded that local lung rest aids the process of healing in pulmonary tuberculosis and is directly responsible in some instances for the collapse of cavities.

It became evident that the cavity walls may coalesce without actual healing taking place. This was demonstrated not only in the two cases just described above but also in Case 10 in which a large sized cavity collapsed on immobilizing lung therapy but promptly opened on slight activity. Obviously, further experience is required to determine the length of treatment as well as the nature of follow-up therapy in cases of advanced pulmonary

tuberculosis with cavity. The essential point of the present discussion, however, is to point out that closure of cavities did actually take place as a specific effect of immobilization of both lungs and in cases unsuitable for or unresponsive to other methods of treatment. It is obvious that extensive investigation of this procedure is necessary before any appraisal of its value in various types of pulmonary tuberculosis can be offered. The management of the 12 cases treated by the author is not intended as an ideal of treatment, since mistakes were admittedly made, but should be understood as a groping for knowledge in an exploratory study. The conclusion that the procedure presented may in some cases accomplish recovery unattainable by any other method of tuberculosis therapy is stated with conviction, not in the temperament of dogmatism, but in the hope that other investigators may be stimulated to employ local lung rest therapy.

In two earlier studies of advanced or moderately advanced pulmonary tuberculosis, in which patients lived continuously in an oxygen chamber<sup>10</sup> or resided in a filtered air room,<sup>11</sup> neither clinical recovery nor marked improvement took place in either group. The criteria for selection of these patients, the source of the clinical material, the type of food, nursing care, hospital and medical management were in the main comparable to that employed in the series of cases now presented. The difference in response to immobilization of the lungs, in comparison to the course of the patients in the two previous reports, was striking. It may be additionally emphasized that the recovery which followed residence in the equalizing pressure chamber occurred in patients who had had a prior period of bed rest without significant change in the condition, and that the favorable response to this therapy was not due to a change from one hospital to another.

The chamber now has been air-conditioned so that the temperature is capable of thermostatic regulation from the inside.\* Since only outside air is used, there is no expense of maintenance beyond that of the electric current used. The fear that the patient may have claustrophobia has not interfered with its use in any of the cases in which it has been tried. After the patients learned to arrest chest movement they either had no objection to the treatment or actually liked the therapy. When the tuberculous infection cleared on one side, the patients were invariably eager to have the opportunity of a second or third course rather than to submit to thoracoplasty. Temporary discomforts from the ears and sinuses were in all instances no barrier to continuation of treatment. In no case was the therapy terminated at the wish of the patient but always when it was decided that the time had arrived to try convalescent care or to abandon the treatment.

#### SUMMARY AND CONCLUSIONS

Immobilization of the chest wall and diaphragm has been accomplished in the living subject by residence in the equalizing pressure chamber. A

\* The equalizing pressure chamber is manufactured by Mr. John H. Emerson, 22 Cottage Park Avenue, Cambridge, Mass.

normal exchange of oxygen and carbon dioxide is maintained without the movements or the effort of breathing. The mechanism is dependent on the equalization of pressures on both sides of the chest wall. This is achieved by delaying a wave of alternating pressure to the degree required to compensate for the resistance of the nasopharyngeal tracheo-bronchial passage-way.

The procedure of immobilizing both lungs has been under investigation during the past 10 years. Of 12 cases of advanced bilateral and moderately advanced pulmonary tuberculosis, clinical recovery took place in six, marked improvement in one, slight to moderate temporary benefit in three, and no change in two.

Of the six recovered patients one is a recent case now convalescent for only one year. The remaining five patients were observed for variable follow-up periods: two cases for one year, two cases for four years, one case for seven years.

Of the 12 cases eight were given a single course of three to four months for eight to 11 hours daily; three had two courses and one had three courses. (The first patient, who was in the group of single courses, was treated six hours a day for two months.)

That closure of tuberculous cavities is a specific result of immobilization of both lungs has been demonstrated by roentgen evidence of cavity disappearance during treatment, its re-appearance on bed rest following termination of chamber therapy and a repetition of closure of the same cavity by a subsequent course. This sequence of events has been presented in one patient who had two courses and another patient who had three courses of treatment. In a third case collapse of cavity took place in three months and reexpanded to its original size after two weeks of activity.

Control of hospital food, nursing and medical care was afforded in two earlier investigations on the effect of (a) continuous residence in an oxygen room and (b) in a filtered air chamber, both at bed rest. Although some of these cases were quite similar to those in the present series, no comparable clearing of tuberculous infiltration, healing of cavities or clinical recovery took place in either of the two previously reported therapeutic procedures.

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# HEALED SUBACUTE BACTERIAL ENDOCARDITIS: REPORT OF TWO CASES WITH DEATH DUE TO CONGESTIVE HEART FAILURE \*

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EVEN though reported clinical cures of subacute bacterial endocarditis have become more frequent, there is still a remarkable paucity of pathologic confirmation of healed subacute endocarditis.

Before the advent of penicillin, Weiss and Rhodes,<sup>1</sup> Libman,<sup>2</sup> and Hamman<sup>3</sup> reported autopsied cases in which the heart lesions gave evidence of complete healing. Since penicillin has been added to the armamentarium there have been increasing opportunities to study cardiac specimens of patients dying after apparently successful treatment. A very high percentage of these patients had succumbed as a result of cardiac complications. In this group Rosenblatt and Loewe<sup>4</sup> included two of their cases of subacute bacterial endocarditis cured by combined penicillin-heparin therapy which died later in severe congestive heart failure. The heart valves in both cases demonstrated marked deformity but histologic examination and cultures gave no evidence of active bacterial infection. Mokotoff et al.<sup>5</sup> reported another autopsied case in which death resulted from cardiac failure eight months after arrest of the infection. Postmortem examination revealed evidence of healed or healing valvulitis. Dawson and Hunter,<sup>6</sup> Dolphin and Cruickshank,<sup>7</sup> and Bloomfield<sup>8</sup> have each reported one similar autopsied case.

The following two cases reported here illustrate the cardiac difficulties which may arise in patients with healed subacute bacterial endocarditis.

*Case 1.* B. M., a colored woman, aged 30, was admitted to the University Hospital on Dec. 10, 1945 with the complaint of pain in her abdomen, joint pains and swelling of her ankles of three weeks' duration. Her present illness began a year previously during the winter when she had an episode of migratory pain and swelling of the knees, ankles and left shoulder. Without seeking medical attention she voluntarily followed a regimen of bed rest during which the symptoms disappeared. Following this she noticed dyspnea and palpitations on minimal exertion. Two months before admission she began to have night sweats and three weeks before admission noticed she had fever. Two weeks prior to admission she again suffered migratory joint pains involving her knees, ankles and left shoulder. There had been a loss of 30 pounds of weight during the year before admission.

The past history revealed diphtheria at the age of 10, following which a tonsillectomy was done. At 13, an episode of painful and swollen joints necessitated three months bed rest. Several years later she was told by a physician that she had "a leaking heart."

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Physical examination on admission revealed a thin, rather undernourished young colored female lying flat in bed in no acute distress. Her skin was warm and moist and without petechiae or other lesions. Several petechiae were seen in the conjunctiva of the left lower eyelid. There was slight distention of her neck veins. Her



FIG. 1. (Case 1) Scarred aortic valve with area of endocardial fibrosis below valve.

trachea was deviated to the right. The lung fields revealed no abnormalities on percussion and auscultation. Examination of her heart showed a diffuse apical impulse in the left anterior axillary line in the sixth interspace. A diastolic thrill and shock were palpable at the apex. The left border of dullness, determined to exist at the left anterior axillary line, had a prominent auricular projection. The sounds were force-

ful, rhythmic, and rapid. The rate was 108 per minute. The first mitral sound was accentuated and followed by a long soft blowing murmur which merged with a mid-diastolic murmur. At the aortic area there was a soft systolic and short diastolic murmur. The pulmonic second sound was accentuated. The liver and spleen were not palpable and there was no ascites or edema. The temperature was 100° F.,

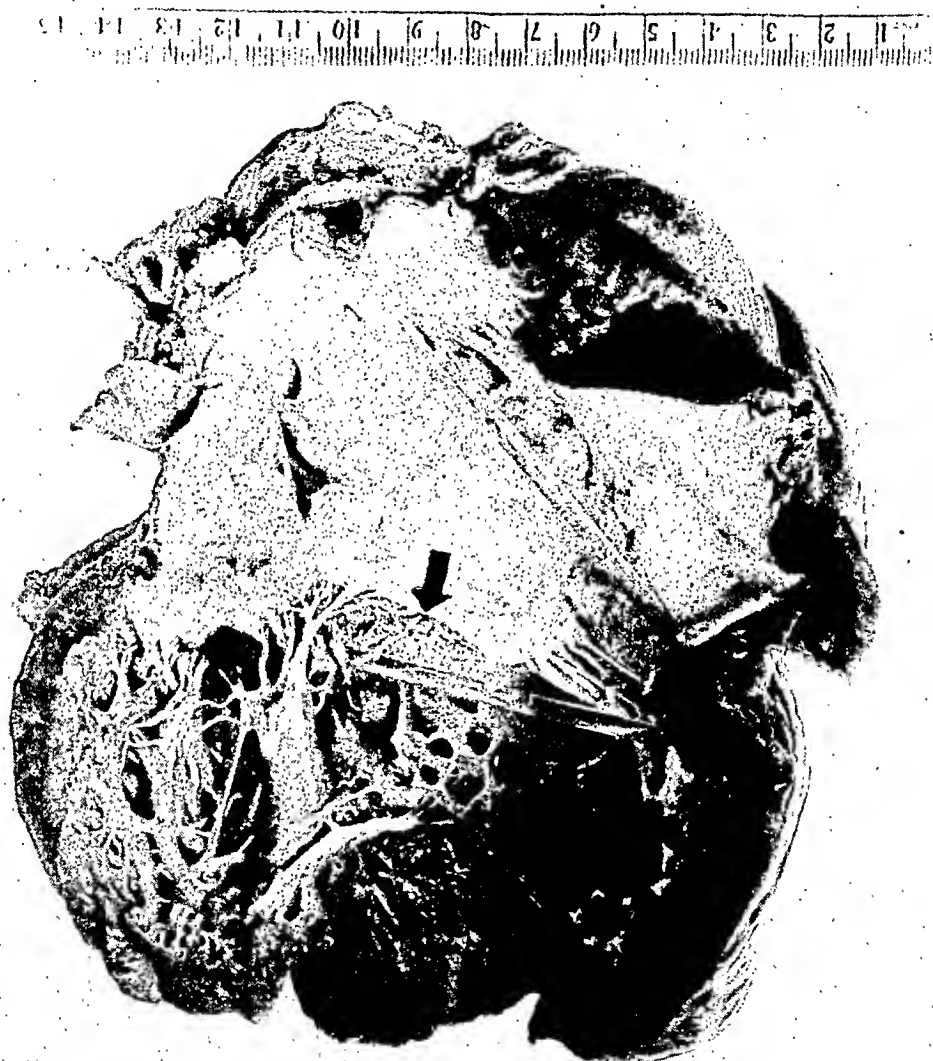


FIG. 2. (Case 1) Mitral valve. Arrow indicates calcified vegetations.

respirations 22, and blood pressure 100 mm. Hg systolic and 50 diastolic. Urinalysis showed a two plus albumin, 8-10 white blood cells and 1-3 granular casts. A hemoglobin of 8.5 gm. per 100 c.c., a red blood cell count of 3,750,000 per cu. mm. and a white blood cell count of 6,400 per cu. mm. were recorded. The differential leukocyte count was normal. Serological tests for syphilis were negative. The sedimentation rate was 28 mm. per hour. Agglutination tests for typhoid, paratyphoid, undulant

fever, and tularemia were negative. The blood urea nitrogen was 18 mg. per 100 c.c. and the carbon dioxide combining power was 20 milliequivalents per liter. Three blood cultures were prepared. Two bore 150 colonies; one, 50 to 75 colonies of *Streptococcus viridans* per c.c. of blood. The electrocardiogram revealed slurred QRS complexes and left axis deviation. A roentgenogram of the chest showed diffuse enlargement of the heart.

On the third hospital day penicillin therapy was begun in doses of 30,000 units intramuscularly every three hours until a total of 15,120,000 units had been given



FIG. 3. (Case 1) Ventricular surface of mitral valve Arrow indicates calcified vegetations.

over a two month period. All blood cultures were negative after penicillin treatment was instituted and the temperature was normal except for an occasional elevation to 99.6° F. The pulse rate varied from 80 to 110 per minute throughout the hospital stay, and the systolic blood pressure varied between 90 and 110 mm. of mercury and the diastolic pressure between 50 and 60 mm. of mercury. With vitamins and ferrous sulfate, the anemia was corrected and the patient's general condition improved. After the penicillin was discontinued the patient walked about without untoward symptoms. The sedimentation rate remained normal. During treatment, the mitral and aortic



murmurs had become louder and the second pulmonic sound more accentuated. A roentgenogram at this time showed the heart to be slightly larger than previously and the lungs to be moderately congested. On March 2, 1946 she was discharged and directed to take prophylactic sulfadiazine. A month after discharge she developed moderately severe congestive heart failure which was treated with digitalis and diuretics. This treatment was unsuccessful. Severe heart failure developed necessitating readmission to the hospital on May 10, 1946.

On this admission, the patient suffered dyspnea, anasarca, and peripheral venous congestion. The heart was enlarged to the left mid-axillary line and 2 cm. to the right of the sternum. A slight thrill at the apex and a marked thrill over the pulmonic area were palpated. Systolic and diastolic mitral and aortic murmurs were heard. The second pulmonic sound was of increased volume. The radial pulse was regular, of Corrigan type, and accelerated to 100 per minute. The liver edge was at the level of the umbilicus. The blood pressure was 140 mm. Hg systolic and 70 mm. diastolic. The temperature was normal. The hemoglobin and red blood cell count were normal. The white blood cell count was 5,050 with a normal differential count. The urine contained albumin and hyaline casts. The blood urea nitrogen was 25 mg. per 100 c.c., and the carbon dioxide combining power was 20 milliequivalents per liter. The erythrocytic sedimentation rate was 7 mm. per hour. The chest roentgen-ray and electrocardiogram showed no significant changes since the previous examination.

The patient was given a neutral-ash diet. The digitalis dosage was adjusted. It was found that she was able to take only 0.1 mg. of Digitaline Nativelle daily because of vomiting with larger doses. Diuretics were moderately successful at first, but gradually lost their effectiveness. Her blood pressure gradually fell from 140/70 mm. of mercury to 110/50 mm. of mercury. The patient's temperature was always normal or subnormal and her pulse varied between 80 and 100 per minute. Two blood cultures exhibited no growth after five days' incubation. On her twentieth hospital day the edema, ascites and dyspnea began to increase. On the twenty-fourth hospital day decompensation was extreme and numerous ventricular extrasystoles appeared. The blood urea nitrogen was 82 mg. per 100 c.c. and the carbon dioxide combining power was 20 milliequivalents per liter. Normal cardiac rhythm was established with quinidine sulfate, but the patient's general condition remained poor and she died in congestive failure and uremia on her thirty-seventh hospital day.

Observations at Autopsy: The body was that of a slightly undernourished young colored woman. There was moderate edema of the dependent portions. When the body was opened, the liver edge was seen to be 6 cm. below the costal margin. The peritoneal cavity contained 700 c.c. of clear straw colored fluid and generalized tissue edema was noted. Each pleural cavity contained about 600 c.c. of straw colored fluid. The right lung was atelectatic and pleural adhesions were discovered at its apex and base.

Lungs: The right lung weighed 360 gm.; the left lung 370 gm. Both showed a moderate degree of congestion and edema, most marked in the lower lobes.

The liver, kidneys and spleen were not remarkable except for congestive changes.

The heart was large, weighing 660 gm. The pericardium was normal. The myocardium was flabby and red-brown in color. The right ventricular wall measured 0.4 cm. in thickness and the left, 1.3 cm. The measurements of the valve circumferences were: Aortic, 8.5 cm.; pulmonic, 9 cm.; mitral, 11 cm. and tricuspid, 12.5 cm. The aortic valve cusps were thickened and rolled and the commissures were adherent. The mitral valve was thickened and nodular. These nodules were arranged along the free edge of the cusps and were the size of wheat grains or smaller. On one of the chordae tendineae of the mitral valve, there were two tiny grape-like clusters of densely scarred calcified material. The pulmonic and tricuspid valves

were normal. In the left ventricle just below the aortic ring a 2 cm. circular patch of fibrous tissue was seen in the endocardium. The aorta showed minimal atheromatous changes.

**Histologic Examination: Heart:** The pericardium displayed no noteworthy histological changes. In the myocardium, particularly in the region of the aortic ring, edema and dense fibrosis were seen. Thick walled vessels coursed from the ring into the valve cusp. Lymphocytes were sparsely distributed in the stroma. The valve cusp was dense and fibrotic. The endocardium was irregularly eroded. Healed vegetations from the chordae tendineae of the mitral valve selected for section were devoid of recognizable bacteria. Organisms could not be demonstrated by the hematoxylin and eosin stain or Glynn's stain for bacteria. The healed vegetations consisted of dense scar tissue traversed by endothelial and thick walled vessels. Extensive deposits of calcareous material were present.

**Case 2.** M. L., a 45 year old white man, was admitted to the hospital on Feb. 8, 1945 with complaints of night sweats, fever, weakness and fatigue. Six weeks before admission, he had generalized aching, felt weak and tired, and had drenching sweats and fever at night. Symptomatic therapy afforded no relief. Several years before this time he had developed a urethral stricture and his symptoms were attributed to this. He was hospitalized for 10 days in January, 1945 and was found to have a daily elevation of temperature. Sulfonamides were given which seemed to lessen his fever and an operative procedure was done for relief of his stricture. Following discharge from the hospital, he continued to have the same symptoms noted at the onset of his illness. He gave no history of rheumatic episodes, chorea, nosebleeds or tonsillitis. In 1941, while hospitalized for ureteral calculus, he was told he had hypertension.

At the time of his admission, the patient was well developed, well nourished and did not appear ill. No petechiae were seen. The heart was slightly enlarged to a point 1 cm. beyond the left mid-clavicular line. A systolic murmur was heard at the mitral area. The pulse was 80 per minute and regular; the systolic blood pressure was 130 mm. of mercury and the diastolic pressure 70 mm. of mercury. Examination of the lungs added no significant findings. The tip of the spleen was palpable two fingers'-breadth below the costal margin. It was soft and not tender. The liver was not palpable. There was no edema. The temperature was 99.2° F.

The urine was normal except for a one plus albumin test. Examination of the blood showed a red cell count of 3,650,000 per cu. mm., a hemoglobin of 56 per cent, and a white cell count of 5,700 per cu. mm., of which 74 per cent were polymorphonuclear granulocytes. The sedimentation rate was 21 mm. in one hour. The serologic tests for syphilis and agglutinations of febrile antigens were negative. Four blood cultures were positive for *Streptococcus viridans*. One hundred and twelve, four, 30, and 16 colonies per c.c. were grown in successive cultures.

The patient was treated with a total of 5,000,000 units of penicillin given in doses of 25,000 units intramuscularly every three hours over a period of 21 days. All blood cultures were negative after institution of penicillin therapy. Within 24 hours after the first dose of penicillin, his temperature became normal and remained so for four days. His temperature then rose to 99-99.6° F. daily for two weeks. Thereafter he was afebrile. On the fifteenth hospital day examination of the heart revealed an aortic diastolic murmur. Two days later the aortic and mitral murmurs were louder and accompanied by a high-pitched systolic whistling sound. Occasional extrasystoles were heard. After the patient's anemia was corrected with blood transfusions and supportive measures, he was discharged on March 11, 1945 with no clinical evidence of decompensation.

After discharge, the patient complained of weakness and a persistent, non-productive cough which was worse at night. He had dyspnea, and "palpitations" in his arms and legs with slight exertion, but no edema. On March 28, 1945, digitalization

was begun, but when an attempt was made to reduce his dosage below three cat units daily the dyspnea and "palpitations" recurred.

The patient was readmitted on April 7, 1945 because of cough and dyspnea. Examination at this time showed slight obesity but no evident distress. The lungs were clear of adventitious sounds. The pulse was regular, of Corrigan type, and 96 per minute. The systolic blood pressure was 160 mm. of Hg and the diastolic, 80 mm. No shocks or thrills were felt over the precordium. The left border of the heart was just lateral to the mid-clavicular line. To and fro blowing murmurs, heard at the apex, were transmitted to the axilla. At the base and over the sternum, a rough blowing systolic murmur and a prolonged musical diastolic murmur were heard. The liver was enlarged, but not tender. A firm spleen was palpable. There was no edema. A blood culture was negative for bacterial growth. The sedimentation rate was 32 mm. in one hour.

The patient's hospital course was uneventful though he was very apprehensive and emotional at all times. His temperature was never elevated and his pulse ranged between 80 and 90 per minute. He was properly digitalized and discharged on April 14, 1945.

Except for weakness, the patient was well for three weeks following discharge. Then he developed moderate dyspnea and mild cyanosis. He was hospitalized in June and again in July, 1945, each time showing an increase in the degree of his cardiac decompensation. He was treated with constant bed rest, digitalis, ammonium chloride and mercupurin without success. At the time of his final hospital admission in October, 1945, he was in Grade IV decompensation and died 17 days after admission.

Permission for autopsy was not given.

### COMMENT

In view of the strikingly good results of penicillin treatment in subacute bacterial endocarditis, it is alarming to note the high frequency of cardiac complications following apparently successful antibiotic therapy. Besides the listed autopsied cases, there have been to date eight other reported deaths due to congestive failure in patients who were clinically free of bacterial infection.<sup>9, 10, 11, 12</sup> Cardiac arrhythmias, coronary accidents and cardiac failures of varying extent have been described<sup>5, 8, 9, 10, 11, 12, 13, 14</sup> as causes of morbidity and mortality in patients relieved of the infectious agent of bacterial endocarditis.

Explanations of the high incidence of cardiac complications have been offered by Bloomfield,<sup>15</sup> Loewe,<sup>16</sup> and Glaser,<sup>12</sup> who suggest that anatomic changes following penicillin therapy in valves which are the seat of vegetations may promote failure. Of course, failure could be due to the cardiac lesions present before the superimposed infection or to the infection itself. However, severe congestive failure in these cases usually develops only a few months after cessation of therapy during the convalescent period. As Bloomfield points out there is no reason to believe that such a high percentage of patients with uncomplicated cardiac lesions would develop failure in so short a period of time. The mere presence of infection alone should not induce such a high incidence of failure. White<sup>17</sup> has stated that congestive heart failure is not often the cause of death in bacterial endocarditis

and rarely is there enough additional damage to the heart muscle from the infection to cause failure directly.

The conclusion that healing of the infection produces valvular deformities and predisposes to cardiac complications has been supported by postmortem findings. All the reported autopsied cases of healed subacute bacterial endocarditis have revealed thickened, scarred, shrunken valves produced by fibrous contraction of healed vegetations. These valves thus become more grossly incompetent than before. This is especially true in cases in which the aortic valve is involved as illustrated by the two cases reported here, where clinically there occurred an increase in the magnitude of aortic regurgitation as the vegetations healed. It is apparent that recovery from subacute bacterial endocarditis not only depends on the sensitivity of the offending organism but also on the amount of valvular deformity produced as healing ensues. Although these developments remain a serious problem in cases of healed bacterial endocarditis, they do not constitute contraindications to penicillin therapy in cases of active infection but reemphasize the importance of early diagnosis and immediate institution of therapy before the valves have been extensively affected.

#### SUMMARY AND CONCLUSIONS

1. Two cases of healed subacute bacterial endocarditis are reported in which death was due to cardiac failure secondary to marked aortic regurgitation.
2. The material in the one autopsied case presented brings to seven the number of reported autopsied cases of penicillin-cured endocarditis.
3. Cardiac complications of healed subacute endocarditis are discussed.

The authors are indebted to Dr. Milton S. Sacks for permission to use Case 2 of this report.

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## VECTORS OF RICKETTSIAL DISEASES \*

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THE vectors of the rickettsial diseases of man belong to four groups of parasites—ticks, mites, lice, and fleas.

Ticks are vectors of the diseases of the spotted fever and boutonneuse fever groups and are certainly involved to some extent in Q fever. Spotted fever includes Rocky Mountain spotted fever of Canada and the United States and the spotted fevers of Mexico, Colombia, and Brazil. Present knowledge suggests that these diseases differ only in epidemiological features relating to the different vector species. Similarly, boutonneuse fever of the Mediterranean region, Kenya typhus, and South African tick-bite fever appear to be identical. They are very similar to the spotted fevers of the New World. The frequent occurrence of a primary lesion or so-called tache-noir at the site of the infecting tick bite is one of the differentiating characters.

Mites are proved vectors of only one rickettsial disease, i.e. scrub typhus or tsutsugamushi disease. Transmission of endemic typhus by mites has been demonstrated experimentally but human cases definitely attributable to mite vectors are unknown.

The vectors of epidemic or European typhus and of endemic or murine typhus are lice and fleas respectively. Experimental infections of epidemic typhus in fleas and of murine typhus in lice have been reported.

Although the human body louse is the vector of trench fever, the rickettsial nature of this disease apparently has not been conclusively established. A suspected rickettsial agent has several times been observed in supposedly infected lice.

With the exception of epidemic typhus, the rickettsial diseases are primarily diseases of animals, and their vectors are parasites of those animals that function in the maintenance and perpetuation of the disease agents in nature. These parasites do not normally attack man. Therefore human infections are accidental since man plays no direct rôle either in perpetuating the disease or in the life cycle of the parasite vectors. In epidemic typhus, on the other hand, no animal source of the disease is known. Man is the only host of the louse.

The epidemiology of the rickettsial diseases is determined to a great extent by the life history, habits, and host relationships of their vectors.

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## TICKS AND THE SPOTTED FEVERS

Ticks are frequently referred to as insects but they are much more closely related to the mites and spiders. They comprise the superfamily Ixodoidea which is divided into the Ixodidae or hard-bodied ticks and the Argasidae or soft-bodied ticks. These common names are based on the presence of a rigid dorsal plate in the ticks of the former group, and its absence in the latter. All proved tick vectors of rickettsial infections to man are hard-bodied ticks although experimental transmission of some of these infections by certain soft-bodied ticks has been demonstrated. The latter are associated primarily with transmission of relapsing fever spirochetes.

The hard-bodied ticks have four stages in their developmental cycle, the egg, larva, nymph, and adult. Up to several thousand eggs per female are laid in some protected place, usually on the ground. The 6-legged larvae attach to suitable host animals, ingest blood, and those of most species drop to the ground when replete. There they transform to 8-legged nymphs. These repeat the sequence of feeding and molting and transform to adults. A host is again sought and after engorging and mating the females lay their eggs. The life cycle usually requires one or two years. Host relationships vary with the stage and species of tick concerned. Immature stages frequently parasitize one kind of host and adults another. In some species one or both of the immature stages molt on the host. The longevity of ticks is remarkable; adults of some species may live as long as three years without feeding. This has an obvious relationship to problems of tick control.

Tick bite is the commonest means by which human spotted fever infections are acquired. Contamination of the skin with crushed tissues of infected ticks has resulted in occasional cases in the United States.

Spotted fever is known to occur in Canada, the United States, Mexico, Colombia, and Brazil. In North America, the disease was first recognized as an entity about 50 years ago in southern Idaho and western Montana. It is now known to exist in 43 of the 48 states. Those from which it has not been reported are Maine, Vermont, Connecticut, Rhode Island, and Michigan. Three species of ticks are known vectors to man in this country, the Rocky Mountain wood tick, *Dermacentor andersoni*, in the Western States, the American dog tick, *D. variabilis*, in the Central and Eastern States, and the lone-star tick, *Amblyomma americanum*, in the South. These and other ticks, notably the rabbit tick, *Haemaphysalis leporis-palustris*, transmit the infective agent among animals in nature.

Spotted fever in Brazil was recognized in 1928 and has been intensively studied. The principal natural vector is considered to be *Amblyomma cajennense* which occurs from southern Texas to Argentina. Larvae, nymphs, and adults of *cajennense* all attack man. It is common on dogs and other domestic animals and also on many kinds of wild animals.

In Colombia, spotted fever was first reported in 1937 when 63 cases, of

which 60 were fatal, occurred in a small valley with 270 inhabitants. Several households were completely wiped out. The vector originally suspected was a soft-bodied tick, *Ornithodoros rudis*, which is common in houses. Studies at the Rocky Mountain Laboratory showed that this tick is unable to transmit the infective agent, yet the rickettsiae were conserved in the tick tissues as long as 343 days and were passed through the eggs to the next generation. Present evidence suggests that the vector in Colombia, as in Brazil, is *Amblyomma cajennense*.

Spotted fever was first reported in Mexico in the States of Sinaloa and Sonora in 1943. The vector is considered to be the brown dog tick, *Rhipicephalus sanguineus*, a species which in recent years has become very troublesome in the United States in dwellings where dogs are kept as pets, in kennels, and in veterinary hospitals. All active stages feed on dogs. In the United States there are very few records of its attaching to man, a fortunate circumstance, for the species is an efficient vector of spotted fever experimentally.

#### TICKS AND BOUTONNEUSE FEVER

Boutonneuse fever was originally described in 1910 from Tunisia. This disease and the later reported South African tick-bite fever and Kenya typhus comprise a group which has been definitely recognized only in southern Europe and the continent of Africa. The vector of boutonneuse fever in the Mediterranean region and of Kenya typhus is the brown dog tick, *Rhipicephalus sanguineus*, and infections in dogs have been reported. In South Africa, the vectors of tick-bite fever are considered to be *Amblyomma hebraeum* and *Haemaphysalis leachi*. The latter is common on dogs. All stages of this tick may harbor the rickettsiae which may be passed by the female through the eggs to subsequent generations as in New World spotted fever vectors.

#### TICKS AND Q FEVER

The epidemiology of Q fever affords one of the most interesting and puzzling problems in the field of rickettsial diseases. The disease has two separate histories, one in Australia, the other in America.

Published information on Q fever in Australia dates from 1937 when a new disease, which had been observed since 1935 in abattoir workers in Brisbane, was reported. Later it was found that cases were also occurring in dairy and forest workers. There was nothing to suggest case to case transmission and when the rickettsial nature of the disease was discovered, search was made for the causative agent in wild animals and their ectoparasites. Cattle were found susceptible and serological tests showed they are naturally infected. However, the occupational distribution of cases indicated that some human infections were being acquired from sources other than cattle and that possibly ticks were involved.



In searching for sources of the disease in nature, bandicoots were found to be naturally infected, also the bandicoot tick, *Haemaphysalis humerosa*. This tick is capable of transmitting infection to guinea pigs and presumably to other animals. The rickettsiae occur in the epithelial lining of the gut, and are present in enormous numbers in the feces. Fecal contamination of the lesion at the site of the tick bite was suggested as the likely mode of infecting the host. However, demonstration of a bandicoot-tick-bandicoot cycle did not solve the problem of human infection for this tick does not attack man, but another tick, *Ixodes holocyclus*, also commonly found on bandicoots, does bite man readily and may be responsible for infections of outdoor workers. It also attacks cattle and thus it may be the means of conveying infection to the common cattle ticks, *Boophilus annulatus microplus* and *Haemaphysalis bispinosa*. Although these two ticks do not attack man, their excrement is highly infectious.

In 1939, 15 cases of Q fever occurred among laboratory workers in the National Institute of Health at Washington, D. C. Inhalation of infected dust was suggested as a possible explanation of the scattered case distribution. Derrick stated that this means of infection may explain the occurrence of cases in abattoir workers in Australia, the source of the infected dust being tick feces from the hides of cattle. This forms a fine powder readily carried by air currents and retains its infectiousness for several months.

Turning now to Q fever in America, we have a much different story. Studies of this disease were begun at about the same time as those of Q fever in Australia. In 1935, workers at the Rocky Mountain Laboratory isolated an agent pathogenic for laboratory animals from *Dermacentor andersoni* collected in western Montana. Tick transmission to laboratory animals and the rickettsial nature of the agent were later demonstrated. It has now been recovered from five species of ticks from widely scattered sections of the United States yet no human cases definitely associated with ticks are known. In fact only three cases other than laboratory acquired infections have been reported, the sources of infection being undetermined.

#### MITES AND TSUTSUGAMUSHI DISEASE

The mites comprise a large group closely related to the ticks but unlike the latter, only a small proportion are animal parasites. Tsutsugamushi disease is transmitted to man by species of the family Trombiculidae, a group represented in America by many species of which one is the common chigger or red bug.

The life history of the trombiculid mites is of special interest in relation to disease transmission since only the larvae are parasitic on animals. Although imperfectly known, the general pattern of the life cycle is about as follows: eggs are deposited in the soil; the almost microscopic larvae feed on vertebrate hosts of many kinds, become fully engorged in a few days and drop to the ground; the nymphal and adult stages live in the soil. Almost

nothing is known of their food habits. It is apparent then that the disease agent must pass from the larvae of one generation through the non-parasitic nymphs and adults to the larvae of the next generation. That this occurs was recently proved experimentally by the India-Burma field party of the United States of America Typhus Commission when laboratory-reared larvae from females collected in nature produced scrub typhus infection in a white rat on which they were fed.

*Trombicula akamushi* and *T. deliensis* are proved vectors of scrub typhus to man. Eventually, other species may be incriminated.

The classification of trombiculid mites is in a very unsettled state at the present time and opinions differ as to limits of species variation. Collections from scattered geographical areas indicate that *akamushi* and *deliensis* are quite variable. Thus *T. fletcheri* incriminated by Blake et al. as a vector in New Guinea may be only a local variant of *akamushi*. Similar variants of *deliensis* have also been found.

The important natural hosts of vector mites are rats and other small wild mammals prevalent in endemic areas. Scrub typhus infections have been demonstrated in wild rats in New Guinea, Federated Malay States, Assam, and Burma, in tree shrews in Burma, and in the field vole in Japan.

#### LICE AND EPIDEMIC TYPHUS

The lice are a distinctive group of ectoparasites containing about 150 species. Only two kinds infest man, the pubic louse, *Phthirus pubis*, and the head and body louse, *Pediculus humanus*. The varietal names *capitis* and *corporis* are applied to the scalp infesting and to the body infesting forms respectively. The pubic louse has not been incriminated in disease transmission and only the body louse is generally considered to be important in this regard.

Body lice usually infest the seams of clothing in close contact with the body in regions such as the crotch, waist line, armpits, the neck and shoulders. The female deposits from 275 to 300 eggs which are glued to the fibers of the cloth and rarely to the body hairs. The eggs hatch in about 10 days and the young undergo three molts before reaching the adult stage some two weeks later. The cycle from egg to egg may be completed in a month under favorable conditions. Lice feed frequently and when removed from the host will die of starvation in a few days. Uncleanliness and the close crowding of individuals especially in sleeping quarters favor the increase and spread of lice.

Lice become infected by feeding on typhus patients. The rickettsiae appear to be present in the cells of the epithelial lining of the midgut rather than in the salivary glands and after a few days they may occur abundantly in the feces. Present evidence suggests that the feces are the principal source of infection for man. Loeffler and Mooser in 1942 list the possible modes of infection as follows: (1) the rickettsiae contained in the feces or

crushed tissues of lice may enter through abrasions of the skin, (2) they may be introduced by the mouth parts of the louse contaminated with infected feces, (3) rickettsiae contained in the feces or bodies of lice may be rubbed onto the conjunctiva by fingers which have been contaminated with infected louse feces or tissues, and (4) infective feces may be inhaled in the form of dust.

So far as is known, the rickettsiae are not transmitted by infected lice to their offspring.

It has been suggested that infected feces may be a factor in the conservation of the rickettsiae during interepidemic periods.

Epidemic typhus is widely distributed in many parts of the world. Although isolated outbreaks have occurred in this country, the disease has not become established nor is this considered likely in the future in view of the negligible incidence of lousiness in the population and the highly satisfactory delousing measures which have been developed.

### FLEAS AND ENDEMIC TYPHUS

Fleas are such common insects that little description of them seems necessary. About 600 species are known, all parasites of mammals and birds. They are not strictly host specific although generally speaking each species is commonly associated with some particular species of host or species group. Much of our knowledge of the biology and host relationships of fleas has resulted from study of fleas in relation to bubonic plague.

Fleas are parasitic in the adult stage only, feeding briefly and intermittently on appropriate hosts. The adults live mostly in the nests and other sites frequented by their hosts. Eggs are deposited in these places primarily, and the resulting maggot-like larvae feed on dried flea and animal excrement mixed with dust. The adults appear after an intervening pupal stage. The time required for completion of the cycle is greatly influenced by temperature and humidity and ranges from two weeks to several months. The ability of fasting fleas to survive for long periods is of much practical importance.

Endemic or murine typhus occurs as a natural infection of rats and certain other rodents and evidence suggests that it is transmitted among them by their fleas, lice, and mites. The rat fleas, principally *Xenopsylla cheopis*, are considered to be the important vectors to man. Rickettsiae have not been seen in the salivary glands of fleas and transmission by bite has not been demonstrated. Flea feces are highly infectious and it is likely that transmission to man occurs in much the same way as in European typhus.

Murine typhus is widespread in many regions of the world, mostly in warm climates. In the United States, it is endemic in the South and occurs sporadically in some of the more northern states. The rising number of reported cases is focusing attention on this disease as one of our important public health problems.

In conclusion, it is desired to point out that the rôle of vectors in the maintenance and dissemination of rickettsial infections in nature and in their transmission to man is still far from fully explored. At the present time, new disease agents of this group and their means of transmission are being studied in such widely separated countries as the United States, Australia, and Russia. This is a fascinating and fertile field of research in which the combined efforts of physicians, bacteriologists, entomologists, zoölogists, and scientists working in the related fields are required for the solution of many of the problems encountered.

#### APPENDIX

Since this paper was presented the discovery of a new mite-borne disease entity, rickettsialpox, in New York City has been reported. An outbreak of Q fever involving 55 of 136 slaughterhouse workers and stock handlers in Amarillo, Texas, has also been reported. Epidemiological investigations revealed that cattle were probably the source of the human infections. No evidence was obtained suggesting that ticks or other arthropods were involved.

# KALA-AZAR IN THE UNITED STATES: REVIEW OF THE LITERATURE AND REPORT OF TWO CASES: STILBAMIDINE TREATMENT \*

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KALA-AZAR (visceral Leishmaniasis) is a disease now demanding a higher index of suspicion among physicians in the United States. Although only nine cases have been reported in the United States up to the present time, the possible presence of kala-azar must be considered in returned veterans exhibiting unexplained fever. The report presented here emphasizes this point, records two cases diagnosed at the U. S. Marine Hospital, New Orleans, La., and discusses treatment with stilbamidine for the first time in this country.

McKhann, in a personal communication to Packchanian,<sup>1</sup> reported in 1937 the case of an Italian boy developing symptoms in Boston, Massachusetts, and diagnosed by culture of *Leishmania donovani*. The patient apparently contracted the disease in Italy. The second case was a Chinese student exhibiting clinical evidence of the disease about three months after entering the United States. Diagnosis was confirmed by splenic puncture, and cure effected with fuadin and neostam.<sup>2</sup>

Rose<sup>3</sup> recorded the case of a 15-year-old Filipino girl from Calcutta, India, who was diagnosed in New York by demonstration of Leishman-Donovan bodies in smears from sternal bone marrow. She had been resident in the United States one year. The Letterman General Hospital (U. S. Army), San Francisco, Calif.,<sup>4</sup> admitted a 35-year-old white male staff sergeant in 1944 following an undiagnosed febrile illness of three months' duration, with onset after three months' service in China. The patient died, and diagnosis was made by demonstration of *Leishmania donovani* in material from the liver and spleen.

Price and Myer<sup>5</sup> contributed the fifth case, that of an Indian seaman hospitalized at the U. S. Marine Hospital, Ellis Island, N. Y., where diagnosis was made by splenic puncture and neostibosan administered with apparent cure of the disease. Sweeney, Friedlander, and Queen<sup>6</sup> submitted an unusual case of abdominal pain and splenomegaly in an Italian prisoner-of-war serving in this country, in whom the diagnosis of kala-azar was made only following splenectomy for suspected splenic anemia.

The seventh and eighth cases were reported from the U. S. Marine Hospital, San Francisco, Calif., by Munter and Packchanian.<sup>1</sup> Both were

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Indian seamen with similar symptoms and physical findings. Examination of smears from the sternal bone marrow revealed Leishman-Donovan bodies in both instances. The organism also was successfully cultured on N.N.N. medium.

Kaminsky and Wever<sup>7</sup> recently reported the case of a 26-year-old white private in the airborne infantry of the AUS, who was admitted to the Borden General Hospital for observation for fever and hepatosplenomegaly. He had been hospitalized in five other Army hospitals for a 10-month illness characterized chiefly by fluctuating temperature, weight loss, anemia, and progressive enlargement of the spleen and liver. He had served 10 months in 1942-43 in North Africa, and nine months in 1943-44 in Sicily and Italy, with onset of symptoms while in Italy. Laboratory findings included elevated total proteins with reversal of the albumin-globulin ratio, anemia and leukopenia, and elevated sedimentation rate. Positive presumptive serological tests for kala-azar led to examination of material obtained by sternal, splenic, and liver punctures. *Leishmania donovani* were identified in spleen and liver tissue; the bone marrow smears were negative. Neostibosan was administered with prompt and satisfactory response.

It seems pertinent to our consideration of kala-azar in the United States to point out that Burchenal and Woods<sup>8</sup> described three cases, and Angevine, Hamilton, Wallace, and Hazard<sup>9</sup> two cases of visceral leishmaniasis occurring in United States servicemen from the Mediterranean littoral, and treated at Army Hospitals in England, accentuating the incidence of this condition in native Americans.

#### ETIOLOGY AND EPIDEMIOLOGY

Kala-azar is caused by *Leishmania donovani*, a protozoal organism of the family Trypanosomidae, with the leishmania form occurring in man and the leptomonad form in vector and culture.<sup>10, 11, 12, 13</sup> Transmission is attributed to flies of the genus *Phlebotomus*, with dogs (especially in the Mediterranean area), man, rodents, and possibly other mammals serving as a reservoir. The bite of the sandfly is generally considered prerequisite to infection, but Southwell and Kirshner<sup>14</sup> contend that invasion may occur in the absence of an actual bite (i.e., mashing the insect, excreta contaminating skin abrasions, etc.). They state that experimental work resulted in no positive infections when only the leptomonad forms were inoculated, that leptomonad forms only are present in the pharynx of the sandfly, and that leishmania forms (present in the mid-gut of the insect) almost invariably produced infection.

Leishman-Donovan bodies have been demonstrated in the nasal discharges of humans, introducing another possible route of dissemination of the disease. Senekjic<sup>15</sup> contends that *L. chagasi* is identical with *L. donovani*, in support of the opinion that American and Old World visceral leishmaniasis are caused by the same etiological agent.

The disease is relatively world-wide in tropical and semitropical zones (figure 1). Kala-azar is found in Asia: Eastern India (Assam, Bengal, Bihar, Madras, and Sikkim), and in China from Peking in the north to Canton in the south, and in southern Manchuria and central Asia. It is endemic in Europe, in southern Russia, Transcaucasia, Turkestan, and the Mediterranean littoral (southern Italy, France, Spain, and the Mediterranean islands). In Africa, infections may be found in Morocco, Algeria,

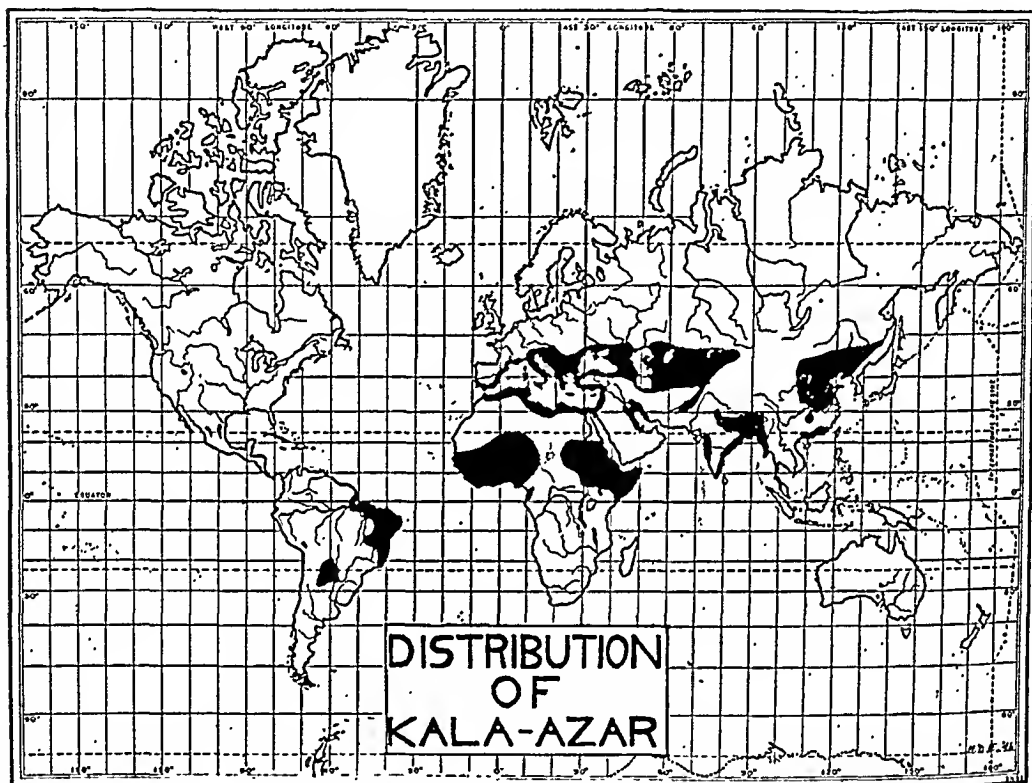


FIG. 1.

Tunis, Tripolitania, Cyrenaica, the Egyptian Sudan (a particularly virulent form), Kenya, French Equatorial Africa, and Nigeria. Kala-azar in the Western Hemisphere is thought to be confined to Brazil, Paraguay, and Argentina.

Both sexes and all ages are affected. The disease is rare at altitudes above 2,000 feet, and practically non-existent above 4,000 feet. The British were keenly aware of this condition in the Mediterranean theater during World War II, issuing special medical bulletins<sup>10</sup> to their armed forces to be on the lookout for cases among their troops serving in this area. The disease occurs most commonly among individuals with lowered vitality due to any cause.

## PATHOLOGY

The generally accepted concept is that the flagellated form is introduced into the human skin with the sandfly as vector. Little is known of the sequence of events from the point of infection to the period of systemic invasion. Reports<sup>8,9</sup> of lymph node involvement suggest that the organism is not introduced directly into the blood but is arrested in the regional nodes, from which it can later spread to the rest of the body.

Christophers<sup>17</sup> is accredited with being the first to give a comprehensive description of the pathology. Subsequent studies in animals and humans by Shortt,<sup>18</sup> Meleney,<sup>20</sup> Hu,<sup>19</sup> and others have added little to the original observations. The parasite is harbored in the aflagellar, rounded or oval-form, by the cells of the reticulo-endothelial system. In these cells acting as macrophages, multiplication of the parasite occurs, with gradual enlargement of the cell until it bursts, pouring its contents into the blood stream, allowing new cells to become infected. The liver, spleen, and bone marrow are particularly involved. Grossly, the liver is usually enlarged and fatty. The organisms are found in the Kupffer cells and periportal connective tissue.

In early stages the spleen is large, soft, and doughy; in later stages it becomes fibrotic. The parasites are found within the reticulum cells, endothelial cells and the lymph follicles. The bone marrow is hyperplastic, containing innumerable macrophages which are the enlarged reticulo-endothelial cells. In the bowel, implantation of the leishmania within the villi and lymph nodes may cause ulcerations, accounting for the diarrhea seen clinically. In lymph nodes there is proliferation of the macrophages, causing lymphadenopathy. Macrophages are also found in the adrenals, kidneys, heart, and testes, and, rarely, in the meninges.

This generalized hyperplasia of the reticulo-endothelial system has been called the clasmatocytic tissue by Meleney.<sup>20</sup> Of particular interest is the fact that the tissue changes can occur even though the parasites are not readily demonstrable in the macrophages.

## CLINICAL PICTURE

Following an incubation period of from two weeks to more than a year (average two to four months), kala-azar exhibits at onset chills, profuse sweats, malaise, and high fever, often with a daily double-rise in the early phases. Not infrequently diarrhea is present. Burke<sup>21</sup> was impressed with epigastric pain and vomiting immediately following meals as the earliest symptom in 2 per cent to 3 per cent of a large series of cases. The spleen and liver then enlarge, the former often reaching tremendous proportions. Weight loss becomes evident despite little impairment of appetite. It progresses to marked emaciation in untreated cases. Grayish pigmentation of the skin, especially the hands, nails, forehead, and central line of the abdomen, may occur.



Striking laboratory findings are the leukopenia (from 2,000 to 4,000), progressive anemia, and changes in the plasma proteins. Sati<sup>22</sup> states that leukopenia is invariably present and eosinophilia invariably absent except with concomitant worm infestation. Total protein levels are elevated,<sup>23</sup> the globulin fraction being increased, with reversal of the albumin-globulin ratio exaggerated by an absolute decrease of albumin, contributing to the late clinical appearance of ascites and edema. The erythrocyte sedimentation rate is increased in all cases.

Diagnosis depends ultimately on demonstration of Leishman-Donovan bodies in body fluids or tissue, through identification in smears, isolation in culture on N.N.N. medium<sup>1</sup> or inoculation into susceptible animals. Napier<sup>24</sup> thinks splenic puncture yields the highest percentage of positive smear examinations. Workers in India and the Sudan have had extensive experience with this procedure without accident. Liver puncture is occasionally resorted to. The authors think, however, that as sternal puncture is so safe and simple a technic, it is to be preferred for use in the United States because bone marrow offers almost as high a percentage of positive smears as material from the spleen; and sternal puncture also may be repeated a number of times without hazard to the patient. Lymph node biopsy may be helpful, by either demonstrating the parasites in section, or from smears or culture. Peripheral blood smear examination is said to result in identification in 60 per cent to 70 per cent of cases. This figure is thought to be too high. Moreover search for the organism in the blood is time-consuming, and difficult. For these reasons, this method is impractical. Dr. A. J. Walker,<sup>25</sup> of the Tulane University School of Tropical Medicine, suggests study of thick smears as a more rapid means of parasitic identification in peripheral blood in kala-azar, with a probably higher percentage of positive findings.

Presumptive diagnosis may be made on the basis of positive euglobulin, formol-gel, and antimony tests, if the clinical picture is compatible. Differential diagnosis includes: Malaria, aleukemic leukemia, typhoid, brucellosis, tuberculosis, amebic disease, enteric infections, tularemia, bilharziasis, trypanosomiasis, and subacute bacterial endocarditis.

*Case 1.* S. M., a 46-year-old Indian seaman from Calcutta, was admitted to the U. S. Marine Hospital, New Orleans, La. on Nov. 23, 1945, with a presumptive diagnosis of malaria. The history was unsatisfactory because of language difficulties. Information obtained, however, indicated that the patient had left Calcutta three months previously and had been ill aboard ship for about two months with fever, bloody diarrhea, nausea, anorexia, and weakness. He was said to have had "Indian malaria" in the past. Syphilis was denied. Further inquiry was completely unsatisfactory.

Physical examination revealed an emaciated, dehydrated, obviously anemic Indian male appearing older than the stated age. Weakness and evidence of marked recent weight loss were apparent. Temperature on admission was 37.2° C., pulse rate 96 per minute, and blood pressure 85 mm. Hg systolic, 55 mm. Hg diastolic. Pertinent findings included questionably icteric sclerae, slight bilateral inguinal

lymphadenopathy, a markedly enlarged, movable, moderately firm, slightly tender spleen which extended about 10 cm. below the costal margin, and a slightly enlarged liver.

Laboratory data: Hemoglobin 8 gm. per cent; red blood cells 2.5 million per cu. mm.; white blood cells 3,000 per cu. mm.; 72 per cent neutrophils, 52 per cent being band forms. Anisocytosis, poikilocytosis, and polychromatophilia were noted. No malarial parasites could be demonstrated. Urinalysis revealed a moderate albuminuria (100 to 200 mg.) and a few finely granular and leukocyte casts. Agglutinations for typhus and brucellosis were negative. The Wassermann test was anti-complementary and the Kahn test was negative. Repeated malaria studies (thick and thin smears) before and after adrenalin-provocative technic, were consistently negative. Icterus index was 15 units. Stool examination revealed 4 plus occult blood but no other abnormal findings. A second leukocyte count on Nov. 27 was 3,400 per cu. mm., with the differential count as before. No eosinophils were seen. The erythrocyte sedimentation rate (Wintrobe) was 46 mm./hr. with hematocrit of 24 per cent. Roentgen-ray of the chest was normal. Total proteins equalled 5.37 gm. per cent, with globulin 2.40 and albumin 2.97 gm. per cent. Formol-gel and euglobulin tests were positive. The Weltmann sero-coagulation test gave a value of 9.

Course in hospital: The night following admission, the patient's temperature rose to 39.6° C. and continued high for several days (figure 2). The patient was treated expectantly with fluids, whole blood transfusion, and massive vitamin therapy while diagnostic studies were being carried on. Penicillin was administered (after negative reports from the malaria studies) because of the critical condition of the patient. Laboratory studies being negative except for anemia and leukopenia, a sternal puncture was done the fourth hospital day. Examination of the marrow smears disclosed Leishman-Donovan bodies. This finding was confirmed by Dr. A. J. Walker, of the Tulane University School of Tropical Medicine.

Meanwhile, the patient's condition appeared to be improving somewhat after three days of penicillin (160,000 units a day). On November 30, the patient being much better, it was decided to do a splenic puncture to further confirm the diagnosis and attempt to evaluate the response to treatment; antimony was being withheld temporarily as the patient appeared to be improving on penicillin. Accordingly, splenic puncture was performed under sterile precautions on December 1. The patient stood the procedure well, but about six hours thereafter became very restless, apprehensive, and obviously in pain. Examination at that time showed abdominal distention and tympany without spasm or rigidity. Temperature was then 37.8° C. and pulse 96 per minute. The patient died about 45 minutes after the onset of symptoms.

Autopsy was performed four days after death. The body had been refrigerated and was in a fair state of preservation. It was that of a moderately emaciated Hindu weighing approximately 100 pounds. The skin was dry; the superficial lymph nodes were not enlarged. When the abdominal cavity was opened about 4,000 c.c. of a thin, bloody fluid were found. The spleen was considerably enlarged. On its anterior margin was a small, clean, puncture wound measuring about 1 mm. In the lungs, bronchopneumonia with overlying pleurisy was found in the right upper lobe and scattered patches of bronchopneumonia were found over the entire lung. The lymph nodes throughout the body and in the mediastinum were small. The liver was slightly enlarged, flabby, and fatty. The spleen weighed 1,030 gm. The pulp was red, soft, and bulged above the cut surface. In the lower portion of the ileum the lymph follicles were prominent; Peyer's patches were enlarged. Small, superficial hemorrhagic ulcers were found in the rectum. The brain was edematous but showed no significant changes. Leishman-Donovan bodies were identified in liver, spleen, and bone marrow, both from direct smears and in paraffin sections. Other organs

showed the clasmatoctytic response with proliferation of macrophages throughout the entire body, but Leishman-Donovan bodies were not found, except in the above-mentioned organs.

Case 2. J. F. McD., a 24-year-old white male veteran of the service forces of the AAF, a native of Louisiana, was admitted to the U. S. Marine Hospital, New Orleans, La., on February 9, 1946, with a diagnosis of "fever of undetermined origin," having been referred from another hospital where treatment with sulfa-

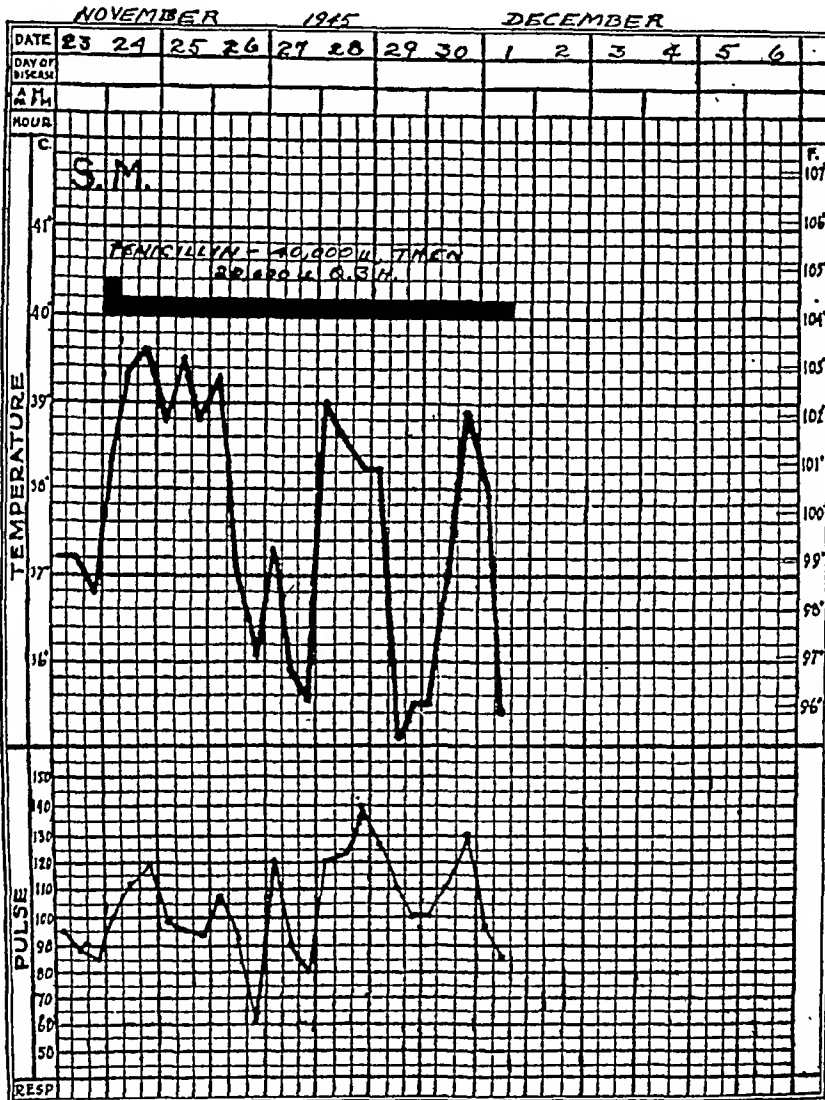


FIG. 2. Temperature chart, case 1, S. M.

diazine, penicillin, and quinine had failed to alter the course of a high, intermittent, and remittent fever of some two and a half months' duration.

The patient had served 13 months at an Army installation about 90 miles from Calcutta, India. Four months before leaving India, he was under observation for two weeks for a swollen gland in the right inguinal region; no diagnosis was made, according to the patient, and the swelling subsided. He left India in May 1945, and returned to the United States via Tinian, Guam, and the Hawaiian Islands, arriving

home and, being discharged from the service in December 1945. His past history was negative except for appendectomy in 1943.

On admission to this hospital, the patient stated that on December 22, 1945, he experienced a sudden onset of profuse sweats and fever to 103° or 104° F. which continued nightly until the time of examination. Three shaking chills had occurred at scattered intervals. Appetite was relatively unimpaired, and the patient felt fairly well during the daytime. Despite this, there had been approximately 20 pounds weight loss since the onset of symptoms. Occasional mild bouts of diarrhea had occurred during the preceding 12 to 18 months; otherwise systems review was essentially negative. A communication from the referring hospital stated that during his two weeks in that institution, extensive laboratory studies had been negative or normal except for *Strongyloides stercoralis* larvae in the stools (white blood count

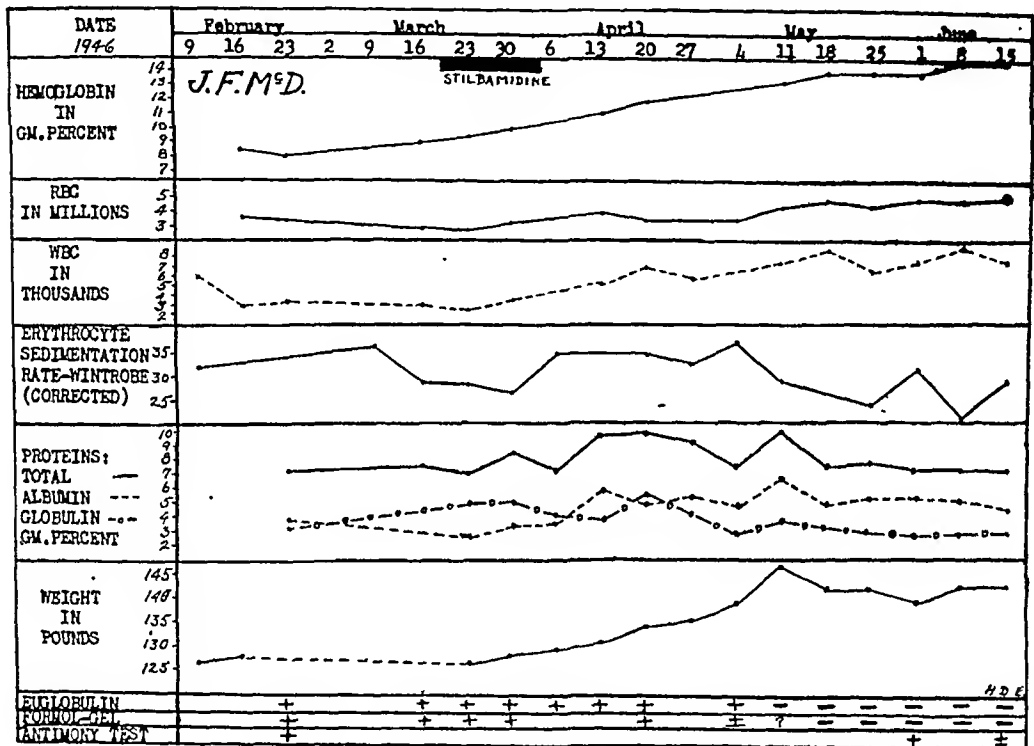


FIG. 3. Chart of significant laboratory data, case 2, J. F. McD.

was 6,400), and that the physical examinations done between January 22 and February 7, 1946, had been normal except for fever and evidence of weight loss.

Initial physical examination in the New Orleans Marine Hospital on February 9, 1946, revealed a small but well-developed white male weighing 126 pounds, appearing chronically ill. Temperature was 38.3° C., pulse rate 112 per minute, and blood pressure 110 mm. Hg systolic, 65 mm. Hg diastolic. Pertinent findings included moderate shotty cervical lymphadenopathy, palpable epitrochlear and axillary nodes, palpable slightly tender liver, a questionably palpable spleen, and an old right McBurney incisional scar. Recalling Case 1 described above, the intern's admission impression was visceral leishmaniasis.

Laboratory data: The more important laboratory findings are outlined in figure 3. Urinalyses were normal throughout. Stool examinations revealed the presence of *Strongyloides stercoralis*. Repeated thick and thin malaria smear studies were negative. Agglutinations for the typhoid-paratyphoid group, typhus, tularemia, and

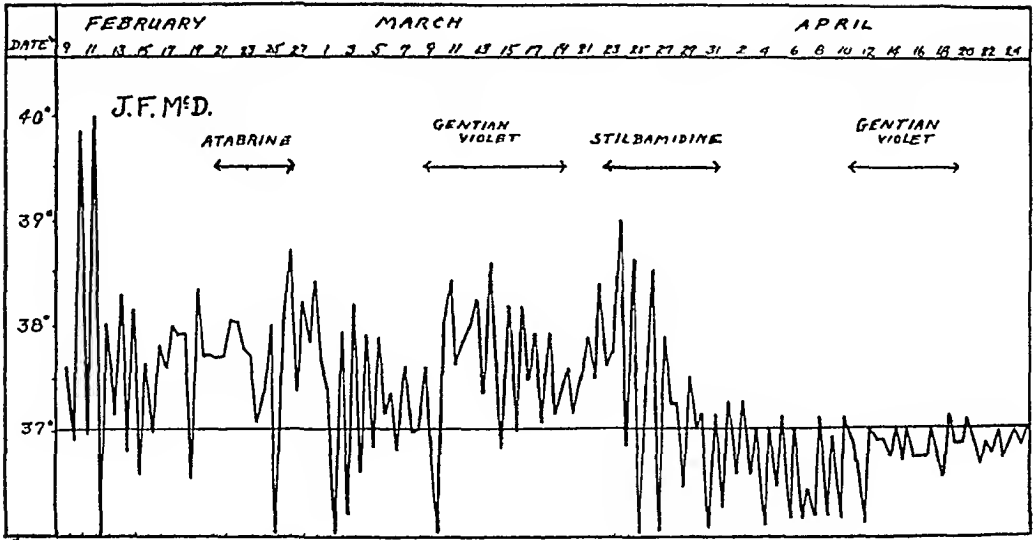


FIG. 4. Temperature chart, case 2, J. F. McD.

brucellosis were not abnormal. Wassermann and Kahn tests were negative. Blood cultures were sterile on several occasions. Prothrombin time prior to treatment ranged from 50 per cent to 60 per cent of normal. Takata-Ara test reaction read  $\text{OOO}++++$ . Roentgenogram of the chest was normal, as was the electrocardiogram.

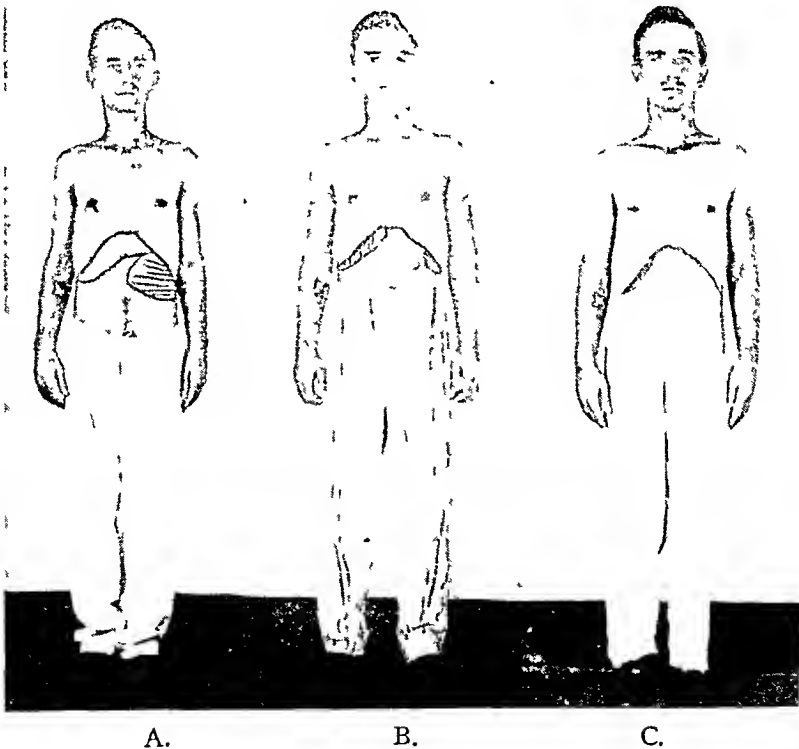


FIG. 5. J. F. McD. before and after treatment. A. Before treatment. B. Four weeks after treatment. C. Ten weeks after treatment.

Course in hospital: Kala-azar being suspected on admission, studies were directed to substantiate our impression. Malaria was ruled out by intensive blood studies. Slight eosinophilia was explained by the presence of intestinal parasites, which were eliminated after two courses of gentian violet. The liver and spleen enlarged progressively over a period of about six weeks prior to institution of trypanocidal therapy (figure 5), the spleen descending about 10 cm. below the costal margin, and the liver becoming palpable about 4 or 5 cm. down. Therapeutic trial on atabrine failed to influence the temperature curve. Sternal marrow punctures were done February 13 and February 25 without finding Leishman-Donovan bodies. Biopsy of the epitrochlear node on the left was done March 1. Grossly, the lymph node was slightly



FIG. 6. Leishman-Donovan bodies from case 2, sternal marrow smear. (Photomicrograph made through the kindness of Dr. Joseph Ehrlich, Lebanon Hospital, N. Y. C.)

enlarged. On microscopic examination the normal architecture was lost. There was a generalized replacement of the node by large macrophages and reticulum cells. Leishman-Donovan bodies were not found either on smear or paraffin sections. Material from bone marrow and lymph node was inoculated intraperitoneally into hamsters. Studies from this have not yet been completed.

In the meantime, the patient's condition remained essentially unchanged clinically; he continued with fever, profuse sweats, and insomnia, but without other symptoms (figure 4). On March 14, Dr. I. Snapper, of Mt. Sinai Hospital, New York City, was consulted on the case. He repeated the presumptive tests for kala-azar and the sternal puncture. Many *Leishmania donovani* were identified in smears from this marrow by Dr. Snapper. One week later, treatment with stilbamidine (4-4" diamidino stilbene\*) was initiated, the patient receiving 25 mg. in 10 c.c.

\* Obtained through the courtesy of Chieſ Willard W. Wright, Sanitarian Director (R), Zoology Laboratory, National Institute of Health, U. S. Public Health Service, Bethesda, Md.

sterile distilled water intravenously the first day, 50 mg. the second day, and 100 mg. daily thereafter for eight doses, totalling 875 mg.

The patient's course during and after treatment was uncomplicated, temperature returning to normal, spleen and liver diminishing in size, and blood abnormalities readjusting towards normal values (figure 3). Sternal bone marrow examination on April 17, 17 days after completion of treatment, failed to reveal the parasites. The patient was discharged May 3, in good health, and was thereafter followed as an out-patient. To date no evidence of relapse has appeared. The spleen is no longer palpable, and the liver edge barely so.

### TREATMENT

Since 1912 the pentavalent antimony compounds have carried the burden of specific therapy for kala-azar. Originally tartar-emetic was used; then Stibacetin, Stibosan, Neostibosan, Urea stibamine, Antimosan, Stibamine-glucoside (Neostam), Aminino-stiburea, Solustibosan and sodium antimony gluconate were developed, converting the mortality from about 90 to 95 per cent in untreated cases to 2 to 5 per cent of those treated with specific trypanocidal agents.<sup>10, 11, 12</sup>

Aromatic diamidines have more recently assumed a position of increasing importance in the treatment of visceral leishmaniasis. Extensive studies on absorption, toxicity, excretion, and effectiveness of the dihydrochloride and the isothionate of 4-4'' diamidino stilbene (Stilbamidine), both in experimental animals and in clinical series have been carried out by workers in India and the Sudan.<sup>26, 27, 28</sup> Stilbamidine was found to possess the greatest trypanocidal activity of a large group of aromatic diamidines.<sup>29, 31, 32, 34, 36, 38</sup> It was 100 times more effective than neostibosan in inhibiting the growth of flagellates of *Leishmania donovani* in culture.<sup>30</sup> Adams et al.<sup>33</sup> and Napier and coworkers<sup>35, 37</sup> found this group of drugs extremely effective in human cases. It has not been used previously for treatment of kala-azar in the United States.

Stilbamidine is very unstable in aqueous solution on exposure to light, and rapidly loses its therapeutic activity together with assumption of marked increase in toxicity.<sup>39, 40</sup> Intravenous injection of the drug usually produces a transient fall in blood pressure, with the patient exhibiting one or more of various symptoms attributable to the circulatory imbalance.

Freshly prepared solution is indicated; epinephrine (0.25 c.c. of 1:1,000 sol.) may be given intramuscularly prior to, or held in readiness at the time of injection.<sup>21, 41</sup> Late (one to three months) toxic effects include sensory aberrations of varied nature (more commonly affecting the trigeminal nerve), neuritis, mental derangements, and occasionally hepatic failure with death; but there have been no reports of delayed toxic reactions following injection of *freshly* prepared solution. Stilbamidine is considered therapeutically more effective than the pentavalent antimony compounds<sup>21, 42</sup> and is of value, particularly in resistant cases.

Criteria of cure are: Absence of fever, increase in weight, return of hemogram and proteins to normal, and reduction in the size of the spleen and liver.

Relapses occasionally occur. Of the relapses 95 per cent occur within four months, and 99 per cent within six months. In such cases stilbamidine is indicated, provided at least one month has elapsed since the completion of the first course of treatment.

### DISCUSSION

Exogenous visceral leishmaniasis is being reported with increasing frequency in the United States, because of the increase in amount and rapidity of world travel, and more particularly, the return of great numbers of veterans of the armed forces from the various endemic areas. This fact should stimulate awareness in American physicians of the possibility of kala-azar in patients complaining of symptoms or exhibiting signs consistent with such condition. The usually lengthy incubation period allows introduction into the United States of many cases which may be discharged from the armed forces in apparently good physical condition. Such possibility will remain prominent many months after the withdrawal of the last of our occupation forces.

The diagnosis may be suspected in patients presenting symptoms and/or findings of fever, weight loss, anemia, leukopenia, abnormal proteins, and spleno- or hepatomegaly. Confirmation depends on identification of the Leishman-Donovan bodies by means of culture, blood, or tissue examination. It is recommended that repeated sternal marrow studies be done before resorting to splenic or hepatic puncture, as it appears that the parasite occurs in colonies or groups, and one or more marrow smears may yield negative results even in the hands of experienced examiners. Sternal puncture is an easy, safe, and relatively painless procedure, whereas entry into intraabdominal organs is not without danger, as demonstrated in our first case. Treatment with pentavalent antimony compounds or stilbamidine is highly effective. The latter drug offers hope of cure of cases failing to respond to the pentavalent antimony group, and also in those cases caused by the apparently more virulent strains found most commonly in the Sudan. Toxicity with either drug is low when proper precautions of administration are observed.

### SUMMARY

1. Nine cases of exogenous visceral leishmaniasis (kala-azar) are reviewed and two additional cases reported.
2. With extended epidemiological studies, it becomes apparent that kala-azar is endemic throughout a much wider area than previously generally known.
3. Attention is focused and emphasis placed on the likelihood of increasing occurrence of kala-azar in the United States, and American doctors are warned to maintain a high index of suspicion for this condition in patients who have been resident in endemic areas.



4. Clinical and laboratory findings are presented, together with criteria (presumptive and absolute) for diagnosis.

5. Repeated sternal marrow examination is advocated before resorting to splenic or liver puncture, with discussion of our reasons therefor.

6. Treatment consists of administration of pentavalent antimony compounds or stilbamidine, an aromatic diamidine with a high therapeutic index of trypanocidal activity. Clinical pharmacology of stilbamidine is briefly outlined.

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# ASPIRIN ALLERGY: ITS RELATIONSHIP TO CHRONIC INTRACTABLE ASTHMA \*

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FOR some time we have recognized a rather characteristic type of asthmatic patient whose symptoms are of unusual severity and chronicity, and who in addition presents a history of hypersensitivity to aspirin. Aspirin allergy has long been recognized, and a number of reports of severe reactions, some fatal, have appeared in the literature.<sup>1</sup> The present discussion, however, does not deal particularly with these acute reactions to aspirin, but rather with the relationship of this drug hypersensitivity to the etiology of the chronic asthma which these individuals display.

We have reviewed the findings in 45 private patients who fall into this category. From the histories it was well established in each that the ingestion of a small amount of aspirin would result in an immediate severe paroxysm of asthma. Yet it is hardly possible to incriminate aspirin as the agent responsible for the persistent chronic intractable asthma which occurs apart from the acute episodes following the ingestion of the drug. There appears to be, however, more than a casual relationship between aspirin allergy and this type of chronic asthma, since each of the patients in the group presents many features in common. In addition to unusual severity and chronicity, practically all display an associated nasal allergy with a high incidence of polyposis; common occurrence of emphysema; eosinophilia in the blood as well as the bronchial and nasal secretions; usual absence of skin reactions to specific agents which might explain the chronic asthma; a poor prognosis of the asthma, which not infrequently has a fatal outcome.

Acute allergic manifestations other than asthma, frequently occur from aspirin. Urticaria and angioneurotic edema are commonly encountered, and we have also seen several cases of vasomotor rhinitis, abdominal cramps, and one case of eczema related to aspirin ingestion. Instances of purpura and migraine have also been reported. The manifestation produced by aspirin is not always the same as the patient's chronic allergic complaint. We have seen six patients with asthma and vasomotor rhinitis in whom aspirin produced urticarial eruptions. Prickman and Buckstein<sup>2</sup> have likewise observed that the reaction is not always similar to the patient's presenting allergy. This discussion concerns only those patients whose primary complaint is asthma, and in whom the ingestion of aspirin results in an acute exacerbation of the asthma.

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*History:* Seventeen males and 28 females comprised the group of 45 patients studied. Their ages ranged from five to 62 years, 70 per cent of the cases occurring in the age group from 30 to 50. Familial allergy of some type was ascertained in 33 cases, but no history of aspirin allergy in other members of the family was established. In no instance was aspirin sensitivity the principal reason for seeking medical aid or advice. Its presence was either volunteered by the patient or elicited by direct questioning. The drug allergy in almost every instance was discovered by the patient some time after the appearance of chronic asthma. In most instances it could be recalled that aspirin was well tolerated prior to and for periods of six months to 27 years following the onset of asthmatic symptoms, when suddenly the ingestion of the usual dose produced a severe paroxysm which proved difficult to relieve. Two patients attributed their first attack to aspirin, following which the asthma became chronic. One of the latter cases suffered from severe vasomotor rhinitis for two years before asthma developed. Most patients had associated nasal symptoms which antedated the asthma by some period of time, and 67 per cent had already undergone some form of nasal surgery when first seen. One patient experienced his first asthmatic episode following the removal of nasal polyps. Approximately 20 per cent believed their first attack followed a respiratory tract infection. As a general rule, asthma became chronic shortly after its onset. Seasonal accentuations coincident with a pollen or mold season occurred in some instances. Thirteen patients gave a history of sensitivity to drugs other than aspirin. The drugs identified were aminopyrine, codeine, morphine, quinine, phenacetin, atophan and ipral. Aminopyrine, phenacetin and atophan produced asthma, while the remainder resulted in urticarial reactions.

*Physical Examinations:* The general appearance of these patients is rather typical. They are usually thin and pale, display almost continuous asthma and are compelled to use some form of symptomatic medication almost continually. Emphysema is a common finding, and was well marked in approximately half of our patients at the time they were first seen by us. It appears to develop in a relatively short period of time after the onset of asthma.

All but five patients had an associated vasomotor rhinitis for which the majority had been subjected to some form of nasal surgery in the past without lasting benefit to either the nasal condition or the asthmatic symptoms. Most of the operative procedures consisted of the removal of polyps, while a smaller number were antrum operations, submucous resections, and turbinectomies. The relationship of nasal polyps to allergy is an interesting one. Kern and Schenck<sup>3</sup> found that approximately 30 per cent of asthmatics have nasal polyps, the incidence being highest in perennial asthma, and lowest in seasonal cases. The relative scarcity of polyps in non-allergic respiratory disorders led them to believe that all so-called "mucous polyps" are of

allergic origin. Hansel<sup>4</sup> is in agreement with this view, and believes that infection is usually a secondary factor. On the other hand, Grove and Cooke<sup>5</sup> maintain that such hyperplastic growths are due to a primary bacterial infection with resultant sensitization to the bacterial products. Hyperplastic changes in the sinuses develop first, while asthma occurs secondarily. In the present study, at least 21 patients, or 46.3 per cent, had nasal polyps. Since not all patients had a thorough examination of the nose it is possible that the incidence of nasal polyps is even higher.

*Laboratory Examinations and Skin Tests:* Examination of the sputum was carried out in 23 cases; and eosinophiles were found to be the predominant cellular element in 73 per cent. Nasal smears in those patients with associated rhinitis almost always showed the presence of eosinophiles. Blood smears were made in 32 cases, and contained from 3 to 22 per cent eosinophiles. More than half of the smears showed a count over 5 per cent (table 1).

TABLE I  
Blood Eosinophiles in 32 Patients

Eosinophiles Per cent	Number of Patients
3-5	10
6-10	14
11-15	5
16-20	2
21-25	1

Skin tests with the common inhalant and food allergens were carried out in 42 patients (table 2) and were entirely negative in 26. One or more skin

TABLE II  
Results of Skin Tests in 42 Patients

Number of Patients Reacting	Dust	Epidermals	Food	Pollen	Mold
26	0	0	0	0	0
6	+	0	0	0	0
2	+	0	0	0	+
2	0	0	0	+	+
1	+	0	0	+	0
1	+	0	0	+	+
1	+	+	0	+	0
1	0	+	+	+	0
1	+	+	0	0	0
Total 42	12	3	2	6	5

reactions were obtained in 16 patients, the majority reacting to house dust, pollen, and molds, with a smaller number to foods and epidermal substances. In most instances, patients reacting to pollens and molds gave histories of increased symptoms during the periods when these allergens are in the air. Two patients reacting to seasonal allergens failed to show any reactions which could be responsible for their perennial symptoms. Only 14 patients

reacted to non-seasonal allergens which could conceivably be responsible for their chronic difficulty. Van Leeuwen<sup>6</sup> likewise noted a relative paucity of positive skin tests in this type of patient, and reported that cutaneous and intracutaneous tests with foods were always negative.

Cutaneous tests with aspirin, sodium salicylate, and methyl salicylate were entirely negative. Intradermal tests were not attempted because of the inherent danger of severe reactions from minute doses of aspirin. One patient complained of marked nasal stuffiness following a scratch test with the drug. In 1917, Cooke<sup>7</sup> stated that skin reactions to aspirin do not occur as a rule in clinically sensitive individuals except in those in whom a clinical history of urticaria is presented. He found that bronchial reactions to related drugs such as salicylic acid, benzoic acid, antipyrin, sodium acetate and methylsalicylate did not occur. Prickman and Buckstein,<sup>2</sup> in testing two aspirin sensitive patients with a 1:1,000 solution by the scratch method, found a negative response in one who had asthma, while the other whose difficulty was urticaria gave a weakly positive reaction. Coca and Grove<sup>8</sup> found that some patients clinically sensitive to aspirin and quinine gave positive cutaneous reactions to these substances, but a positive passive transfer with the serum of these individuals was not obtained. The failure of drugs to react on the skin is usually explained by the concept of the small molecule or imperfect antigen. However, in a limited series of tests with aspirin conjugates we also failed to obtain positive skin reactions.<sup>9</sup>

*Treatment:* The acute episodes directly caused by aspirin were difficult to relieve. Management of the chronic asthma has been successful in some cases, although in the majority the progress of the asthma has not been stopped. Most patients who demonstrated skin sensitivity to environmental allergens were definitely benefited by their removal, or by desensitization. Of 16 patients who gave positive skin reactions, attention to these factors resulted in moderate to considerable improvement in 12, while five patients showed no appreciable benefit. On the theory that these patients might be sensitive to the salicylate radical of aspirin, several were placed on diets free of salicylate containing foods for varying periods of time without appreciable change in their condition. Some investigators believe that it is the acetyl radical which is responsible for reactions from aspirin. We were able to show later that aspirin sensitive patients could tolerate sodium salicylate.

In those patients who failed to give skin reactions to any allergens, management has been difficult. In view of the prominent infectious element in many, treatment with autogenous and stock respiratory vaccines was administered. We were able to attribute very little benefit to this form of therapy. Sulfonamides and penicillin were likewise ineffective in several cases in which they were tried. On the supposition that the infectious element might be the primary, or at least a contributing factor to their asthma, 12 patients moved to a warm dry climate beneficial to respiratory infections. Four of these felt they were decidedly improved, while eight reported that climate had no effect on their condition. Histamine injec-

tions were given in a few patients but produced no benefit. A course of roentgen-ray therapy over the lungs resulted in definite improvement over a period of months in the four patients to whom it was administered.

### DISCUSSION

Many years ago Van Leeuwen<sup>6</sup> assigned a special significance to aspirin sensitivity as an indicator of the severity of the asthma. He estimated that more than 10 per cent of severe asthmatics are sensitive to aspirin. Grove and Cooke<sup>5</sup> are of the opinion that aspirin sensitivity occurs only in "infective" cases. It is apparent that there is some connection between severe chronic asthma and drug sensitivity, of which aspirin is the most common example, due probably to its extensive use. The concept has long existed that simple chemical substances are incapable of reacting with antibody unless previously joined in some manner to a larger molecule. That such a conjugation between the small molecular constituent (hapten) and body protein may occur to form a new antigenic complex is supported by the work of Landsteiner and his associates.<sup>10</sup> A mechanism such as this might then explain the absence of immediate whealing reactions to chemical compounds. Since aspirin may repeatedly produce severe episodes of asthma yet fail to give a positive skin reaction, it appears logical to suspect that the chronic symptoms encountered in these cases may be due to continued or repeated exposure to substances of a simple chemical nature which because of some difference in the immunologic mechanism are incapable of giving a skin reaction. It is possible that aspirin sensitivity is merely an indication that the individual has acquired the mechanism to react to simple chemical compounds. Such substances could conceivably be present in the diet, or some environmental factor as smoke, paint, or chemical fumes.

Occasionally a low molecular compound is encountered which in sensitive subjects produces immediate whealing skin reactions. Kern<sup>11</sup> reported the case of a chemist working with phthalic anhydride who developed asthma and rhinitis, and who gave whealing scratch reactions to the chemical. More recently Feinberg and Watrous<sup>12</sup> described a group of chemical workers who became sensitive to chloramine, and who showed immediate whealing scratch reactions and transferrable antibodies. These unusual instances demonstrate that the immunologic mechanism of drug allergy may not be far removed from that encountered in the usually recognized protein sensitization. Landsteiner's classic experiments<sup>10</sup> have proved that chemical compounds which are not complete antigens may be combined with larger molecules *in vitro*, and when injected into animals produce antibodies specific for the simple component.

It has been a common practice to blame "intrinsic" agents for those instances of obvious allergic disease where a definite exogenous factor cannot be identified. In many cases, a specific extrinsic agent has later been found which removes these patients from the "intrinsic" category. There are

many strong adherents to the belief that skin test negative cases of asthma are practically synonymous with "infective asthma".<sup>13</sup> In these instances it is claimed that sensitization occurs to bacterial products arising from infection in the sinuses, nose, throat and elsewhere. Our experience indicates that immediate whealing skin reactions to bacteria are not usually present, nor are circulating antibodies demonstrable. Conclusive evidence as to the existence in these cases of bacterial allergy, both clinically and immunologically, is incomplete. Perhaps, advocates of the concept of "infective asthma" would classify the cases in the present discussion as examples of bacterial allergy. The presence of hyperplastic sinusitis in most, and respiratory infection in many, would tend to support this contention. We have felt, however, that infection, when present, was a precipitating factor in an allergy of extrinsic origin or a complicating factor secondary to allergic pathologic changes, rather than the result of sensitization to bacterial products. The control of infection, however, may frequently assume equal importance in the therapeutic management.

In our opinion the cases under discussion satisfy the criteria necessary to place them in the category of allergic disease. A definite history of familial allergy in approximately 63 per cent is in keeping with its occurrence in atopic disease with positive skin tests and circulating antibodies. The presence of eosinophiles in the bronchial and nasal secretions, and an increased blood eosinophilia in almost all, favors an allergic diagnosis. Associated seasonal allergy with the presence of whealing skin reactions to seasonal and non-seasonal allergens in a fair percentage, indicate that these individuals are of an atopic constitution, possessing the ability to become sensitized.

The importance of this discussion is not so much based on a report of 45 cases of aspirin allergy with chronic asthma, as on the possibility suggested that sensitization to simple chemical substances in many instances may be the cause of allergic reactions where skin tests with the usual protein allergens are negative. In the case of aspirin, we are able to identify its association with acute manifestations. Other chemical substances present in the diet or environment capable of inducing sensitization but unable to give positive skin reactions would be far more difficult to identify. This possibility must be given consideration in all reactions of an allergic nature, where the specific agent cannot be readily ascertained by the usual methods. A history of allergic reaction in the past to an identifiable agent, such as aspirin, may suggest that the individual has acquired the mechanism to react to simple chemical compounds.

#### SUMMARY

1. Allergic reactions to aspirin are commonly encountered. Asthma and urticaria are the most common manifestations, and when they occur are extremely acute in nature and difficult to relieve.

2. The frequent association of aspirin allergy with cases of severe chronic



asthma having a poor prognosis, prompted a review of the findings in 45 patients. A high incidence of familial allergy, emphysema, nasal allergy with polyposis, eosinophilia, and frequent absence of positive skin reactions to specific agents were found.

3. Attention to specific factors where identified, resulted in some improvement. In the majority, where etiological factors could not be determined, management based on the control of associated infectious elements proved disappointing. Non-specific methods of treatment were of limited value.

4. Since aspirin in these patients produces acute episodes of asthma, yet fails to give positive skin reactions, it is suggested that repeated exposure to other substances of a chemical nature, also incapable of giving positive skin tests may be responsible for the chronic asthma encountered in these individuals. Such substances could be present in the diet or environment. Allergy to aspirin may be an indicator that the individual has acquired the mechanism to react to simple chemical compounds. Such a mechanism could explain the many cases of allergic disease in which a specific protein allergen cannot be identified.

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# THE ANOXEMIA TEST FOR CORONARY INSUFFICIENCY \*

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CORONARY insufficiency (with or without the anginal syndrome) may have varying etiologies, which have been summarized by Blumgart, Schlesinger and Davis<sup>1</sup> and Levy.<sup>2,9</sup> It is "that condition in which the coronary arteries deliver less blood than is required for the effective performance of the heart."<sup>2</sup> The coronary reserve is "considered as being reduced by those factors which decrease the supply of blood, or by those factors which increase the myocardial demands."<sup>1</sup> Levy and his co-workers<sup>2,3,4,5,6,7,8,9,10</sup> have devised an objective electrocardiographic anoxemia test to assist in making the diagnosis of coronary insufficiency. This test consists briefly of breathing (without rebreathing), under standard conditions, for 20 minutes or until the onset of pain, a mixture of 10 per cent oxygen and 90 per cent nitrogen. Control and interim four-lead (I, II, III and IVF) electrocardiograms are taken. Any one, or any combination, of the three criteria established by Levy et al.<sup>8,10</sup> indicates a "positive" test. These three criteria are:

1. The arithmetic sum of the RS-T deviations in all four leads (I, II, III and IVF) totals 3 mm. or more.
2. There is partial or complete reversal of the direction of the T-wave in Lead I, accompanied by an RS-T deviation of 1 mm., or more, in this lead.
3. There is complete reversal of the direction of the T-wave in Lead IVF, regardless of any associated RS-T deviation in this lead.

A positive test is regarded as a sign of coronary insufficiency; a negative reaction does not exclude the diagnosis. Pain during a test with a negative result (electrocardiographically), particularly if it appears during the first 10 minutes of induced anoxemia is regarded as affording presumptive evidence of a diminished coronary reserve.

Three fundamental precautions are stressed by Levy et al.<sup>2,5,10</sup> to avoid serious reactions. The test should not be done: (1) in the presence of congestive heart failure; (2) within four months after known cardiac infarction; (3) on the same patient more than once in 24 hours.

There has been some difference of opinion concerning (1) the diagnostic efficacy of the test, and (2) its safety. Katz, Hamburger and Schutz<sup>11</sup> in 1934 reported the effects of generalized anoxemia on 17 normals and six

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cases of angina pectoris. This work was done before Levy's anoxemia test was standardized, but is of interest in its results and conclusions. The electrocardiographic changes produced in the normals, in four of the six cases of angina pectoris, and those occurring during spontaneous or induced attacks of angina pectoris were similar. They stated that "the induction of severe generalized anoxemia throws an undue strain on the heart, especially in patients with cardiac disease, and may be a serious hazard to the patient."

In a report in 1941, Burnett, Nims and Josephson<sup>12</sup> concluded that the test (Levy's anoxemia test) might prove to be of some value in the diagnosis of coronary insufficiency, and that they believed the test to be without danger, if carefully and properly done. In a later report, in 1942, the same authors<sup>13</sup> find, after further study, that 24 (19.2 per cent) of 125 normals gave positive tests, mostly inversion of the T-wave in Lead IVF (criterion 3). Also, nine cases without objective evidence of cardiovascular disease, developed precordial pain during the test. They concluded that such a test would be of doubtful clinical value, that "false" results, both "negative" and "positive" were too frequent to justify the use of the test in clinical diagnosis. They stated that the test could not be considered a routine laboratory procedure devoid of all danger to the patient, that there were unpleasant or alarming symptoms in 16 instances, and that meticulous care and a highly trained team, in hospital, were essential in the clinical application of the test. They used primarily mixtures of 10 per cent oxygen and 90 per cent nitrogen at an altitude of 5,420 feet.

In a discussion of the paper of Burnett et al., Dr. L. N. Katz<sup>13</sup> stated: "Considering the potential hazards of anoxemia, which we also noted several years ago, I feel strongly that patients with suspected coronary disease should not be subjected to this test routinely."

Riseman, Waller and Brown,<sup>14</sup> in 1940, conclude that "changes in the electrocardiogram during generalized anoxemia appear to be of little practical value in differential diagnosis, for the difference between the normal and abnormal responses is not sufficiently marked to avoid serious error; also, judging from the literature, the induction of generalized anoxemia is not without danger, especially in patients with arteriosclerosis of the coronary or cerebral vessels."

Pruitt, Burchell and Barnes,<sup>15</sup> in 1945, used the test in 289 cases, whose clinical evaluation was suggestive of coronary insufficiency in all but seven cases. The diagnosis was not established conclusively in any case prior to performance of the test. The authors worked on the "assumption that a positive test affords conclusive evidence of coronary insufficiency." The seven normals gave negative tests. In the 92 cases with a probable clinical diagnosis of angina pectoris, 53.2 per cent gave positive tests, and 19.6 per cent had pain without positive electrocardiographic tests. Of the group of 82 patients with a history which had few if any features of a true anginal syndrome, one (1.2 per cent) had a positive test. Despite this, the clinician

maintained his original diagnosis of myalgia of the chest wall. In 25 of the 289 tests, one or several unfavorable reactions occurred. In two cases in which a brief period of cardiac arrest occurred, the reaction was regarded as dangerous. The authors state that the test is a means of substantiating a diagnosis of angina pectoris based on fairly convincing clinical evidence, and is not a short cut. They would restrict the test "even among acceptable cases to instances in which (1) serious disagreement regarding diagnosis has occurred and (2) the establishment of a definite diagnosis is of such importance that acquisition of all helpful evidence is imperative." With such restriction, they conclude that "the possible danger to the life of the patient and the expenditure of time, effort and materials by the clinician are justifiable in view of the value of the information that can be obtained."

In a discussion of the paper of Burnett et al.<sup>13</sup> Dr. D. Deeds stated that he had been doing the test on private patients at an altitude of one mile (as had the authors) and had not encountered any untoward reactions even in bonafide abnormals, and did not consider the test dangerous. He suggested, as have Levy and his co-workers,<sup>8</sup> that the untoward reactions encountered by the authors might have been due to the use of 10 per cent oxygen mixtures at altitudes of 1 mile, approximately the equivalent of 8 per cent oxygen at sea level.

Levy et al.,<sup>5</sup> in 1941, noted no positive tests in 115 normal cases. One (5.0 per cent) of 19 patients with hypertension without symptoms or signs of coronary sclerosis gave a positive test. Of 33 patients with suspected coronary sclerosis, 18.0 per cent gave a positive test, and in 36.0 per cent pain occurred during the test. Of 22 patients with coronary sclerosis without angina, 31.0 per cent gave a positive test, and 10.0 per cent experienced pain. Of 73 patients with coronary sclerosis with angina, 55.0 per cent gave positive tests, and 63.0 per cent experienced pain. In this work, criterion 4 (partial reversal of the direction of T in Lead IVF, accompanied by an RS-T deviation of 1 mm., or more, in this lead), which has since been discarded, was still being used. Provided the test was carried out keeping in mind the three precautions noted above, no serious untoward effects were observed. Various unpleasant reactions occurred, but the authors state that none was serious or harmful. They conclude that the test is simple and safe.

Levy, Patterson, Clark and Bruenn,<sup>7</sup> in 1941, studied 137 patients, of whom 25 were normal controls. Positive reactions were not observed in any patient without cardiac disease or severe anemia. The authors observe that "the test is simple and safe, that there have been no serious effects, and that the course of the disease has not been affected unfavorably as the result of repeated tests." In the discussion of this paper, Dr. R. L. Levy stated: "In the course of three years, there has been no evidence of injury to the nervous system in our patients."

Patterson, Clark and Levy,<sup>8</sup> in 1942, using the first three criteria only, observed no positive tests in 136 normals. In 157 cases of coronary

sclerosis, the test was positive objectively in 49.0 per cent, and was presumptively positive (pain) in another 20.0 per cent.

Master, Nuzie, Brown and Parker,<sup>18</sup> in 1944, report using the anoxemia test as a check on the Master "Two-Step" Exercise test. They state that the electrocardiographic changes corresponded almost exactly in both tests, and in the few instances where the tests were at variance, that "clinical experience proved the findings of the 'two-step' to be correct." They consider the anoxemia test much more severe than the exercise test, examples of reactions to the former being peripheral vascular collapse, complete exhaustion, severe nausea and dyspnea. They apparently did not follow the precautions stressed by Levy et al., one of their patients having "suffered a coronary occlusion two months before."

Biörck,<sup>19</sup> in 1946, discussing 350 tests on 326 patients, was favorably impressed with the test as a whole, both as to diagnostic accuracy and safety. Using the original four criteria of Levy et al. (with criterion 1 apparently somewhat inaccurately applied), and using Nylin's<sup>10</sup> modification of the gas-mixture apparatus, he found 3 per cent positive tests in the group without suspected coronary disease, 20 per cent positive tests in the group with suspected coronary disease, and 30 per cent positive tests in the group with probable or certain coronary disease. He seemed to ignore the fact that other conditions besides coronary disease may produce "coronary insufficiency." He noted unpleasant symptoms associated with the anoxemia, but few that were alarming and none that could not readily be controlled. He concluded that "the test has much to offer."

Because of these divergent views concerning the diagnostic efficacy and the safety of the test, we decided to try to reevaluate the latter, using controls and clinically definite cases of coronary insufficiency.

#### MATERIAL

Tests were done on 200 control and 20 abnormal cases. On the latter 20 (all males), a clinical diagnosis of coronary insufficiency was definitely established. All 20 (table 1) had angina of effort. Three of the 20 had a history of old myocardial infarction. All 20 showed cardiac enlargement and/or abnormal electrocardiograms. They ranged in age from 35 to 66. Every case with definite coronary insufficiency was included. None was eliminated. All 20 were carefully studied before the test was done (history, physical, electrocardiogram, roentgen-ray, fluoroscopy).

Of the 200 controls (one female), none had angina of effort. There was no other selection of cases, except that a few who expressed fear of the test were excluded. Cases with heart disease were not excluded. They ranged in age from 19 to 61. Comparison of the two groups by age levels is given in table 2. All had history and physical examination before the test. Many (where possible) had electrocardiogram and radiographic examination before the test. Many (again where possible) had radiographic examination after the test. All controls with positive tests had

TABLE I  
Response of Abnormal Cases

Case	Age	Angina Pectoris?	EKG Test	Criterion	Presumptive Test	Reaction to Test	Diagnoses
1	54	Yes	Positive	1 (4½)	Positive 4 minutes	None	1. Hypertensive and arteriosclerotic heart disease.
2	66	Yes	Positive	1 (4 mm.)	Negative	Slight	2. 2 old infarctions. 1. Hypertensive and arteriosclerotic heart disease.
3	38	Yes	Positive	1 (5½)	Negative	Moderate to severe	2. Chronic cholecystitis and lithiasis. 1. Hypertensive heart disease.
4	50	Yes	Positive	1 (6 mm.)	Positive (12)	None	1. Arteriosclerotic heart disease.
5	63	Yes	Positive	1 (7 mm.) 2	Positive (5)	None	1. Arteriosclerotic heart disease.
6	47	Yes	Positive	1 (3½)	Positive (3½)	Slight	2. 1 old infarction. 1. Arteriosclerotic heart disease.
7	39	Yes	Positive	1 (5½)	Positive (3½)	Moderate	1. Hypertensive and arteriosclerotic heart disease.
8	37	Yes	Positive	1 (3 mm.)	Positive (11)	Slight	1. Arteriosclerotic heart disease.
9	49	Yes	Positive	1 (4½) 2 3	Positive (3)	Moderate	1. Arteriosclerotic heart disease.
10	58	Yes	Positive	1 (6½)	Positive (3½)	None	1. Rheumatic and arteriosclerotic heart disease.
11	35	Yes	Negative	—	Positive 9 minutes	Moderate	1. Arteriosclerotic heart disease.
12	60	Yes	Negative	—	Negative	Moderate	2. 1 old infarction. 1. Rheumatic and arteriosclerotic heart disease.
13	57	Yes	Negative	—	Positive (3)	Slight	1. Arteriosclerotic heart disease.
14	43	Yes	Negative	—	Positive (5)	Moderate	2. Calcific aortic stenosis. 1. Hypertensive and arteriosclerotic heart disease.
15	49	Yes	Negative	—	Positive (7)	Moderate	1. Arteriosclerotic heart disease.
16	53	Yes	Negative	—	Positive (18)	Slight	1. Arteriosclerotic heart disease.
17	40	Yes	Negative	—	Negative	Severe	1. Hypertensive heart disease.
18	40	Yes	Negative	—	Positive (3)	Slight to moderate	1. Arteriosclerotic heart disease.
19	57	Yes	Negative	—	Positive (7)	None	1. Arteriosclerotic heart disease.
20	40	Yes	Positive	1 (5 min.)	Negative	Slight	1. Arteriosclerotic heart disease.

TABLE II  
Classification by Age Groups

Age Groups	Controls (200 cases)	Abnormals (20 cases)
19-21	12	
21-30	108	
31-40	63	7
41-50	14	5
51-60	2	6
61-70	1	2

radiographic examination either before or after the test. There were 14 cases of cardiovascular disease in the control group (tables 3 and 4). There were 70 cases without disease, 43 cases of rheumatoid arthritis and/or spondylitis, 23 cases of malaria, 10 cases of anxiety state, 10 cases of injury or disease of the extremities, and one case each of many other conditions (tables 3 and 4).

TABLE III  
Clinical Diagnoses in Control Group with Negative Tests (191 cases)

Diagnosis	No.	Diagnosis	No.
No disease.....	70	Calculus in right ureter.....	1
Rheumatoid arthritis and/or spondylitis.....	43	Neurocirculatory asthenia, post-scarlet fever.....	1
Malaria, recurrent.....	22	Rheumatic polyarthritis, 1 year previously.....	1
Anxiety state: a. Cardiac neurosis.....	9	Myalgia, muscles left anterior chest wall.....	1
b. Fear of flying.....	1	Trench foot, in convalescence.....	1
Fracture of extremity.....	4	Infectious hepatitis, in convalescence..	1
Gun shot wound of extremity.....	4	Ruptured intervertebral disc.....	1
Dupuytren's contracture, hands.....	1	Ruptured cartilage, knee.....	1
Intraventricular block, indeterminate type.....	1	Gonorrheal arthritis, chronic.....	1
Dislocated elbow.....	1	Osteoarthritis, chronic.....	1
Spondylolisthesis, lumbar vertebrae...	1	Severed extensor tendon, thumb.....	1
Basal cell carcinoma, nose.....	1	Cardiovascular disease:.....	14
Laryngitis, traumatic.....	1	Rheumatic aortic and/or mitral disease.....	6
Perforating injury, right eye.....	1	Generalized arteriosclerosis, mild to moderate.....	3
Lymphoid hyperplasia, oral cavity...	1	Rheumatic polyarthritis and carditis, in convalescence.....	3
Sinusitis, chronic.....	1	Idiopathic arrhythmia, ventricular premature contractions, with pulsus bigemini and trigemini.....	1
Otitis media, purulent, chronic.....	1	Hypertensive heart disease.....	1
Hemangioendothelioma, nose.....	1		
Upper respiratory infection, in convalescence.....	1		
Osteomyelitis, chronic, tibia.....	2		
Fibrositis, chronic, back.....	1		
Myositis, lumbar spine.....	1		

TABLE IV  
Control Cases with Positive Tests

Case	Age	Angina Pectoris?	EKG Test	Criterion	Presumptive Test	Reaction to Test	Diagnoses
1	27	No	Positive	1 (3½ mm.)	Negative	Moderate to severe	1. Rheumatic aortic disease.
2	25	No	Positive	1 (7½)	Negative	Severe	1. Malaria, chronic. 2. Hookworm infestation, chronic, persistent. 3. Anemia, secondary, marked.
3	30	No	Positive	1 (3¾)	Negative	Slight	1. Apical systolic murmur, rough 1st sound, P-R interval 0.20 second.
4	37	No	Positive	1 (3 mm.)	Negative	Slight	1. Prominent left ventricle (fluoroscopy), low T <sub>1</sub> , slightly notched R-4.
5	31	No	Positive	1 (3 mm.)	Negative	Severe	1. Intense emotional reaction (fear).
6	42	No	Positive	1 (3½)	Negative	Slight	1. No disease.
7	32	No	Positive	3	Negative	None	1. No disease.
8	30	No	Positive	1 (5 mm.)	Negative	Moderate to severe	1. Rheumatic mitral disease.
9	21	No	Positive	1 (5½)	Negative	Slight	1. Acute rheumatic polyarthritis, 4 months previously.

## METHOD

Levy's method was used, with modification. The tests were done at approximately 700 feet above sea level, at least two hours after meals, at an average temperature of 70° F. The Heidbrink anesthesia machine (figure 1) was used. Tanks of 100 per cent O<sub>2</sub> and 100 per cent N<sub>2</sub> were used

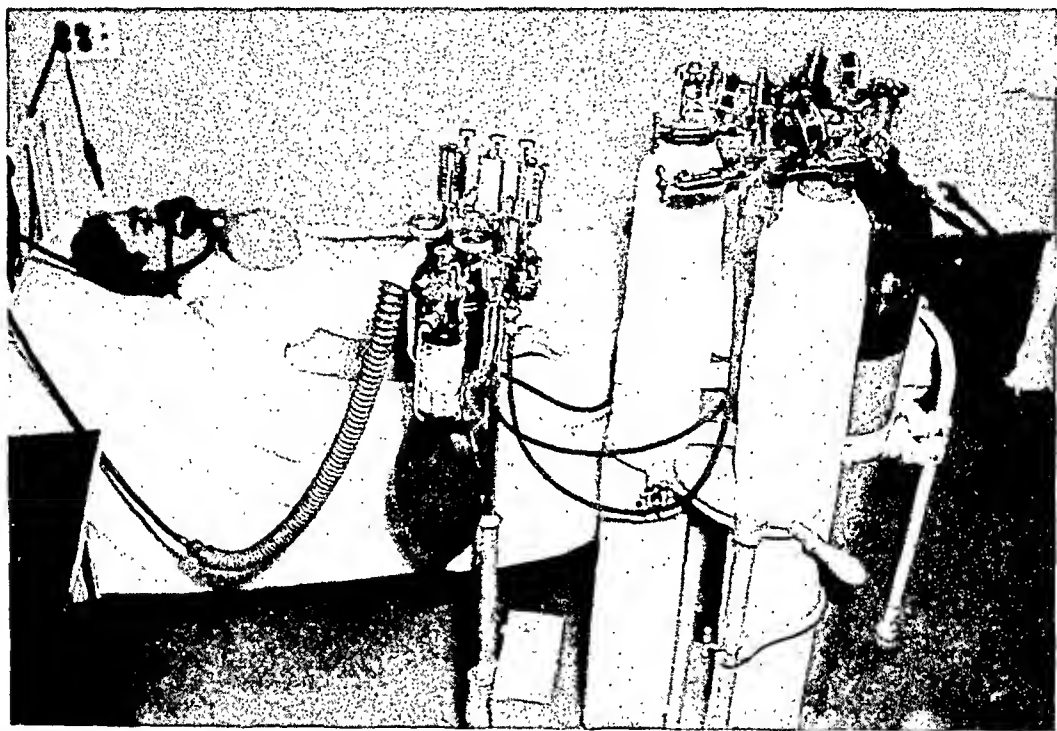


Fig. 1. Apparatus used (Heidbrink anesthesia machine). Electrodes not applied.

(the 10 per cent O<sub>2</sub> and 90 per cent N<sub>2</sub> cylinder was not available), and by means of the gauges a 10 per cent O<sub>2</sub>-90 per cent N<sub>2</sub> mixture was procured. Gas flows of either 1 liter of O<sub>2</sub> and 9 liters of N<sub>2</sub> per minute, or 2 liters and 18 liters respectively, were used, depending on the patient. The machine was checked frequently for leaks. It was not possible to do gas analyses. A reservoir bag and a tightly-fitting mask over nose and mouth were used. There was a one-way valve in the face mask, so that the patient had to inspire the O<sub>2</sub>-N<sub>2</sub> mixture, but could not rebreathe. It was a matter of a few seconds to change from the 10 per cent-90 per cent mixture to 100 per cent O<sub>2</sub>. A humidifier was not used. The test was explained carefully to all patients, and they were instructed to notify us about any type of discomfort by speaking or raising a hand. Pain was not mentioned to the patient as a possible type of discomfort. He rested on a bed, with one pillow, for 5 to 10 minutes, during which time a control four-lead (I, II, III, and IVF) electrocardiogram was taken. The 10 per cent O<sub>2</sub>-90 per cent N<sub>2</sub> mixture was then washed through the apparatus, the mask applied and timed ac-



curately. Frequently, when a patient breathed more deeply, it was necessary to change a 1 liter-9 liter mixture to a 2 liter-18 liter mixture. The flow was continued for 20 minutes, unless pain supervened. Four-lead electrocardiograms were taken at 10 and 20 minutes. The patient was then switched to 100 per cent O<sub>2</sub> for one minute, then permitted to breathe room air for five minutes, at which time a last electrocardiogram was recorded. If pain supervened, an electrocardiogram was immediately taken, the patient switched to 100 per cent O<sub>2</sub> for 1 minute, then room air for five minutes, and a last electrocardiogram taken. The tests were done in a corner of a busy Heart Station office. The impression we tried indirectly to give to the patients was that this was a normal and not unusual procedure. It took two people to do the test, one of whom was the technician. One of us was always present, but as we became accustomed to the test, was often busy at a desk a few feet from the bed, intermittently checking with the patient and the technician. The latter was in constant attendance upon the patient.

### RESULTS

The 20 abnormals (tables 1 and 5) gave 11 (55.0 per cent) positive objective (electrocardiographic) tests. Eight of these 11 cases in addition developed pain, six in less than 10 minutes, and two between 10 and 20 minutes. Seven (35.0 per cent) of the 20 abnormals gave negative objective tests, but developed pain, six in less than 10 minutes and one between 10 and 20 minutes. Two (10.0 per cent) of the 20 abnormals gave negative tests and did not have pain. Of the 20 abnormals, there was a total of 18 (90.0 per cent) positive tests, objective and/or presumptive. Of the 20 abnormals, 13 had abnormal control electrocardiograms. Of these 13 cases, eight had positive objective tests. Of the seven cases with normal control electrocardiograms, three had positive objective tests.

The 200 controls (tables 4, 5 and 6) did not develop pain. Nine (4.5 per cent) gave positive objective tests. In seven of these nine cases (3.5

TABLE V  
Results (Objective and Presumptive) in 220 Anoxemia Tests

Clinical Diagnosis of Angina Pectoris	Negative Objective and Pre- sumptive Tests		Positive Presumptive and Negative Objective Tests		Positive Objective and Negative Presumptive Tests		Both Tests Positive		Total Positive Objective Tests		Total Posi- tive Tests, Objective and/or Presumptive	
	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
Group I Controls (200 cases)					9	4.5			9	4.5	9	4.5
Group II Positive Diagnosis (20 cases)	2	10.0	7	35.0	3	15.0	8	40.0	11	55.0	18	90.0

per cent of the group of 200) there were abnormal cardiovascular, hemic or emotional factors present. In the other two of these nine cases (1.0 per cent of the group of 200) no such factors were present. Exhaustive examination of these nine cases revealed: (1) one case of acute rheumatic polyarthritis four months previously, with presently wandering pacemaker and marked phasic sinus arrhythmia (age 21), (2) one case of rheumatic mitral stenosis (age 30), (3) one case with extremely severe emotional reaction to the test (fear, and mask claustrophobia through previous face-mask sen-

TABLE VI  
The 9 Positive Objective Tests in the Control Group

	Number	% of the Entire Control Group (200 cases)
Abnormal cardiovascular, hemic or emotional factors present	7	3.5
No such factors present	2	1.0

sitization) (age 31), (4) one case with left ventricular enlargement, low  $T_1$  and notched R-IV (age 37), (5) one case with soft apical systolic murmur, rough first mitral sound, and P-R interval of 0.20 second (age 30), (6) one case of moderately severe anemia secondary to malaria and ankylostomiasis (3.17 million red blood cells, 7 grams of hemoglobin), with tachycardia and soft blowing apical systolic murmur (age 25), (7) one case of rheumatic aortic stenosis and insufficiency (age 27), and (8) two cases with no cardiovascular, hemic or emotional factors considered present (ages 42 and 32). One of these latter two cases revealed sinus tachycardia, a slightly low  $T_1$  and a low-normal  $T_2$  (age 32). These two cases (or 1.0 per cent of the control group of 200 cases) may be considered as false positives, or as examples of coronary insufficiency of obscure etiology.

TABLE VII  
Types of Positive Objective Tests (20 cases)

Criteria of Levy	Cases	% of 20 Tests
1. Sum of deviations of RS-T segment in 4 leads is 3 mm. or more	13	65.0
2. Partial or complete $T_1$ inversion plus deviation of RS-T segment of 1 mm. or more	0	0.0
3. Complete reversal of direction of T-wave in Lead IV F	1	5.0
1 and 2	3	15.0
1 and 3	2	10.0
2 and 3	0	0.0
1, 2 and 3	1	5.0

Table 7 breaks up the total number of positive objective tests according to the criteria of Levy; 13 cases (65.0 per cent) of these 20 exhibited criterion No. 1 alone, no cases exhibited No. 2 alone, one case (5.0 per cent) exhibited No. 3 alone, three cases (15.0 per cent) exhibited criteria No. 1 and No. 2, two cases (10.0 per cent) exhibited criteria No. 1 and No. 3,

no cases exhibited criteria No. 2 and No. 3, and one case (5.0 per cent) exhibited criteria No. 1, No. 2 and No. 3. The sums of the deviations of the RS-T segment in those cases with positive criterion No. 1 are as follows (tables 1 and 4) in millimeters: 4.5, 4, 5.75, 6, 7, 3.5, 5.25, 3, 4.25, 6.25, 5, 3.5, 7.5, 3.75, 3, 3, 3.25, 5, 5.5. The one case exhibiting criterion No. 3 alone was one of the two control cases with no disease who gave positive objective tests. The other of these two cases exhibited criterion No. 1 alone.

Patterson, Clark and Levy<sup>8</sup> observed that no case in their series of 136 normals showed a total RS-T deviation greater than 2.5 mm., and in only seven was this figure reached. In some of their cases of coronary sclerosis, the total deviation did not increase in linear fashion, but rose to a peak and then decreased. Our 191 controls who gave negative objective tests showed seven instances where the total RS-T deviation reached 2.5 mm. Of the 211 cases with completed\* (20 minute) tests, 34 showed a total deviation greater at 10 minutes than at 20 minutes.

The 191 controls with negative objective tests exhibited 23 instances where there were T-wave changes, primarily in T<sub>1</sub> and T<sub>4</sub>, consisting of notching, diphasicity, and coming down to or near the iso-electric line. These changes in normals have been noted before.<sup>8</sup> The last electrocardiograms taken (those after 100 per cent O<sub>2</sub> and room air) showed always partial or complete return to the picture seen in the first (or control) electrocardiograms.

Examples of the various types of positive objective (electrocardiographic) tests (table 7) observed are reproduced in figures 2, 3, 4, 5, 6, 7, 8, 9, 10, 11.

TABLE VIII  
Degree of Total Reaction to the Test

Degree	Controls with Negative Tests (191 cases)	Controls with Positive Tests (9 cases)	Abnormals (20 cases)
None	48	1	5
Slight	104	4	6
Moderate	37	0	7
Severe	2	4	2

#### UNPLEASANT SYMPTOMS AND REACTIONS

Total reactions to the test (table 8) excluding presumptively positive tests, were divided as to degree: none, slight, moderate and severe. Of the 191 controls with negative tests, 48 had no reaction, 104 had slight, 37 moderate, and two severe reactions. Of the nine controls with positive tests, one had no reaction, four had slight and four severe reactions. Of the abnormal series of 20 cases, five had no reaction, six had slight, seven moderate and two severe reactions. The types of reaction are shown in table 9, also

divided into degree. The most common symptoms were headache, dizziness, numbness, tingling, drowsiness, air hunger and cyanosis. In two instances among the 191 controls with negative tests, clonic tremors developed, local or generalized. One of these was a 35 year old individual with a cardiac neurosis, who gave negative objective and presumptive tests, and who developed slight generalized twitchings during the last two minutes of the anoxia. He had also had a moderate degree of headache, dizziness, drowsiness, tingling and/or numbness, with fleeting lower chest pains, during the

TABLE IX  
Types of Reaction to the Test

	Controls with Negative Tests (191 cases)			Controls with Positive Tests (9 cases)			Abnormals (20 cases)		
	Slight	Moderate	Severe	Slight	Moderate	Severe	Slight	Moderate	Severe
Headache	50	15		1	1	1	2	2	1
Dizziness	57	23		2	1	1	4	2	1
Numbness	4	6					1	1	
Tingling	45	15		2	1	1	3	3	
Drowsiness	41	18		2		2		3	2
Restlessness	3	2	1			1	1		1
Coldness of feet	2	0							
Air hunger	4	9	1	1		4	1	7	
Cyanosis	15	3						1	
General discomfort	1	2				1		1	1
Abdominal peristalsis	2	0	1						
Fleeting chest pain	7	2	1	1			2	1	
Pounding in ears and/or throbbing of head	2	0		1					1
Weakness	0	3							
Nausea	4	1					1		
Burning and/or congestion of nose, mouth and throat	3	1							
Local or generalized clonic tremors	1	1							
Palpitations	1	0							
Blurred and/or double vision	1	2							
Cough	0	1							
Local or generalized sweating	0	1				2			1

latter half of the test. The other of these two cases was a 57 year old individual with a moderate degree of generalized arteriosclerosis, who gave negative objective and presumptive tests, and who exhibited coarse, circular tremors of the entire left upper extremity during the last 15 minutes of anoxia. He also had slight fleeting pains of the left elbow and hand during the last six minutes of anoxia. Both of these reactions were completely cleared within one minute of breathing 100 per cent O<sub>2</sub>.

In two instances (cases 11 and 18 of the abnormal series) (table 1), both of whom gave negative objective and positive presumptive tests (nine and three minutes respectively), after one minute of 100 per cent O<sub>2</sub> and five

minutes of room air, slight substernal discomfort and generalized weakness still persisted, and were completely relieved by 1/100 grain of nitroglycerine and 10 to 15 minutes of bed rest. These continued reactions may well have been due to the fact that both men were continued in anoxia beyond the initial onset of their pain, case 11 from nine minutes to completion of the

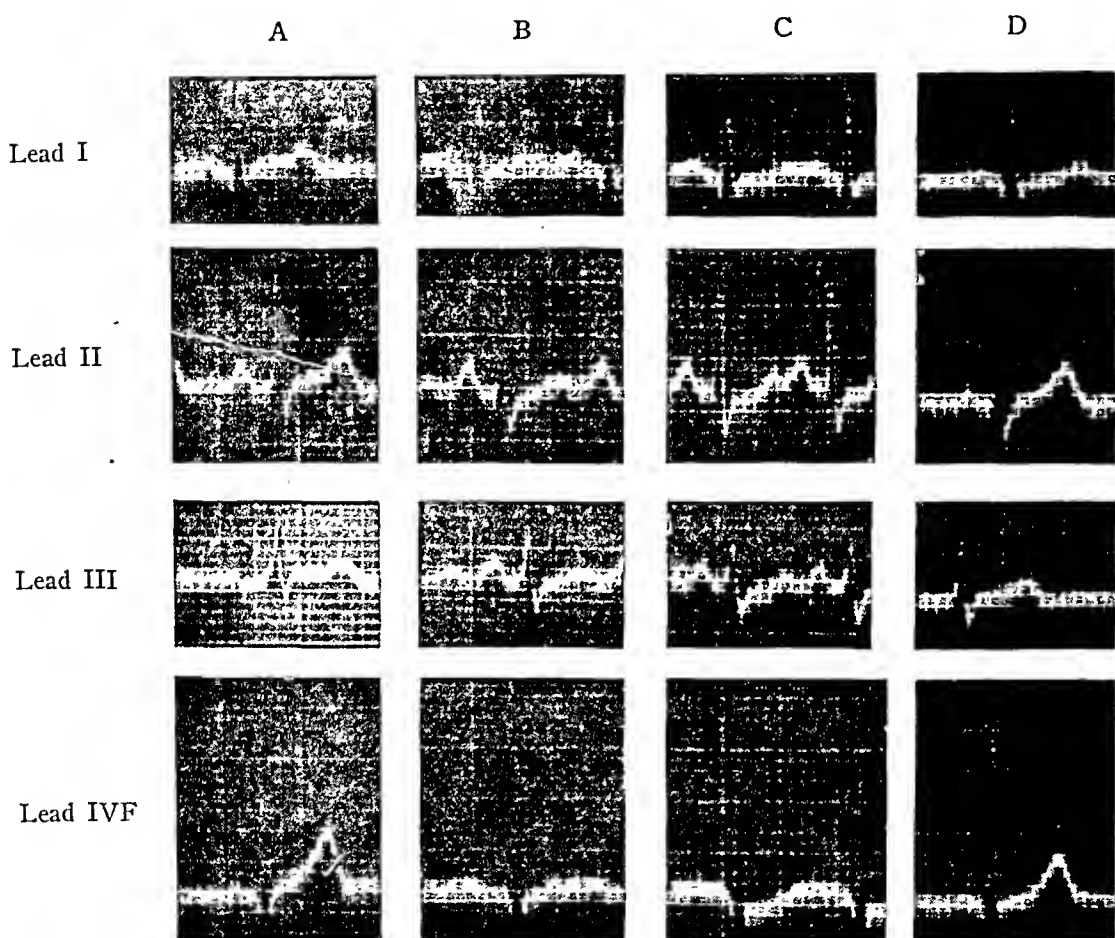


FIG. 2. Case 9 (Table 4). Age 21. Acute rheumatic polyarthrititis, four months previously. A: Control record. B: After 10 minutes of anoxia. C: After 20 minutes of anoxia. D: After 100 per cent oxygen and room air. Criterion 1.

test at 20 minutes, and case 18 from three minutes to nine and one-half minutes. Among the remaining 218 tests there was not a single reaction which did not clear rapidly and completely within the one minute administration of 100 per cent  $O_2$ . No other measures, heroic or otherwise, were necessary.

Fifteen (75.0 per cent) of the 20 abnormal cases gave positive presumptive tests, 12 in less than 10 minutes, and three between 10 and 20 minutes. The pain developed in all instances was exactly like the pain these patients experienced on effort, but was invariably milder in degree. If the anoxia was continued (cases 11 and 18 noted above), the pain either remained

constant (case 11) or increased slowly in severity (case 18). In all instances except these two cases, the pain was completely gone within the one minute duration of the administration of 100 per cent O<sub>2</sub>. Considering the series of 20 abnormal cases, where pain developed and the test was then

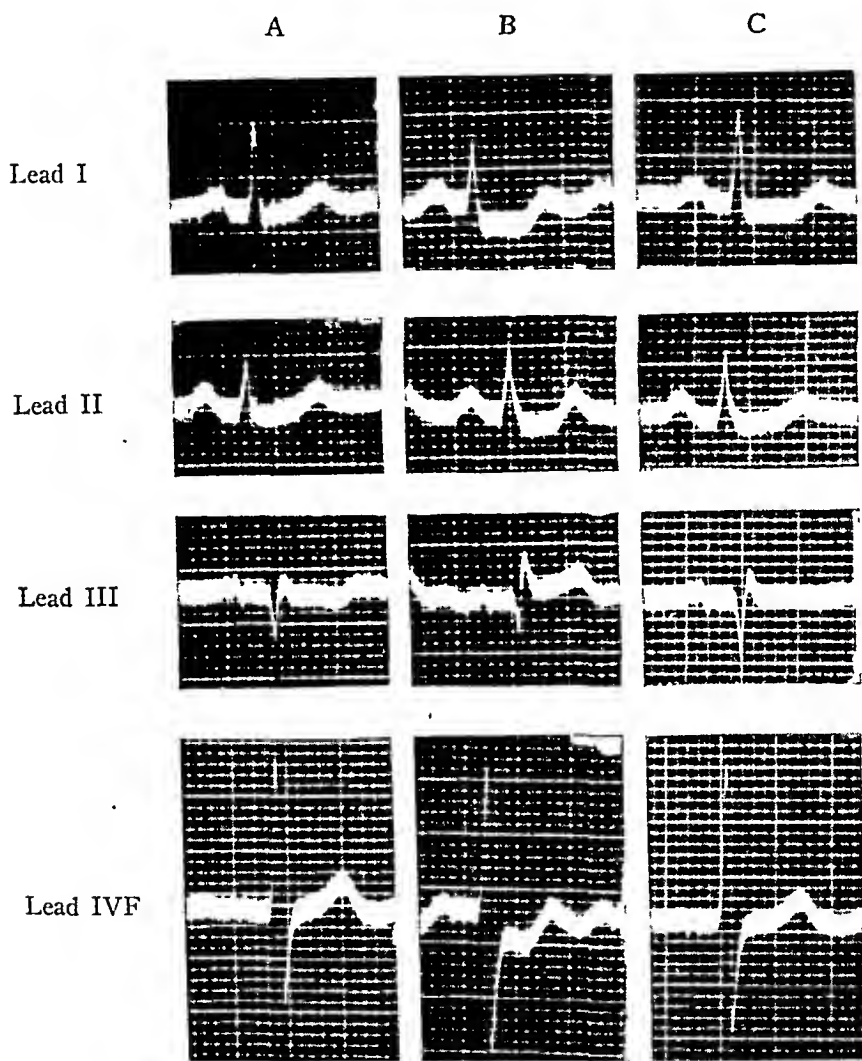


FIG. 3. Case 4 (Table 1). Age 50. Arteriosclerotic heart disease. A: Control record. B: Anginal pain after 12 minutes of anoxia. C: After 100 per cent oxygen and room air. Criterion 1.

stopped, there was not a single instance of a severe reaction, and most had no or slight reactions. It was our impression that those patients with coronary insufficiency who developed pain and in whom the test was then stopped, had in general fewer and certainly less severe reactions than were found in our series of controls with negative tests who all completed their 20 minutes of anoxia. On the other hand, of the nine control cases with positive objective tests, who all had 20 minutes of anoxia, four developed severe reac-

tions. In the two cases of these nine in whom no abnormal cardiovascular, hemic or emotional factors could be found (cases 6 and 7, table 4), the reactions to the test were respectively, "slight" and "none."

Only one test, not included in this series, had to be interrupted by anything other than pain. This was to have been a control who expressed fear

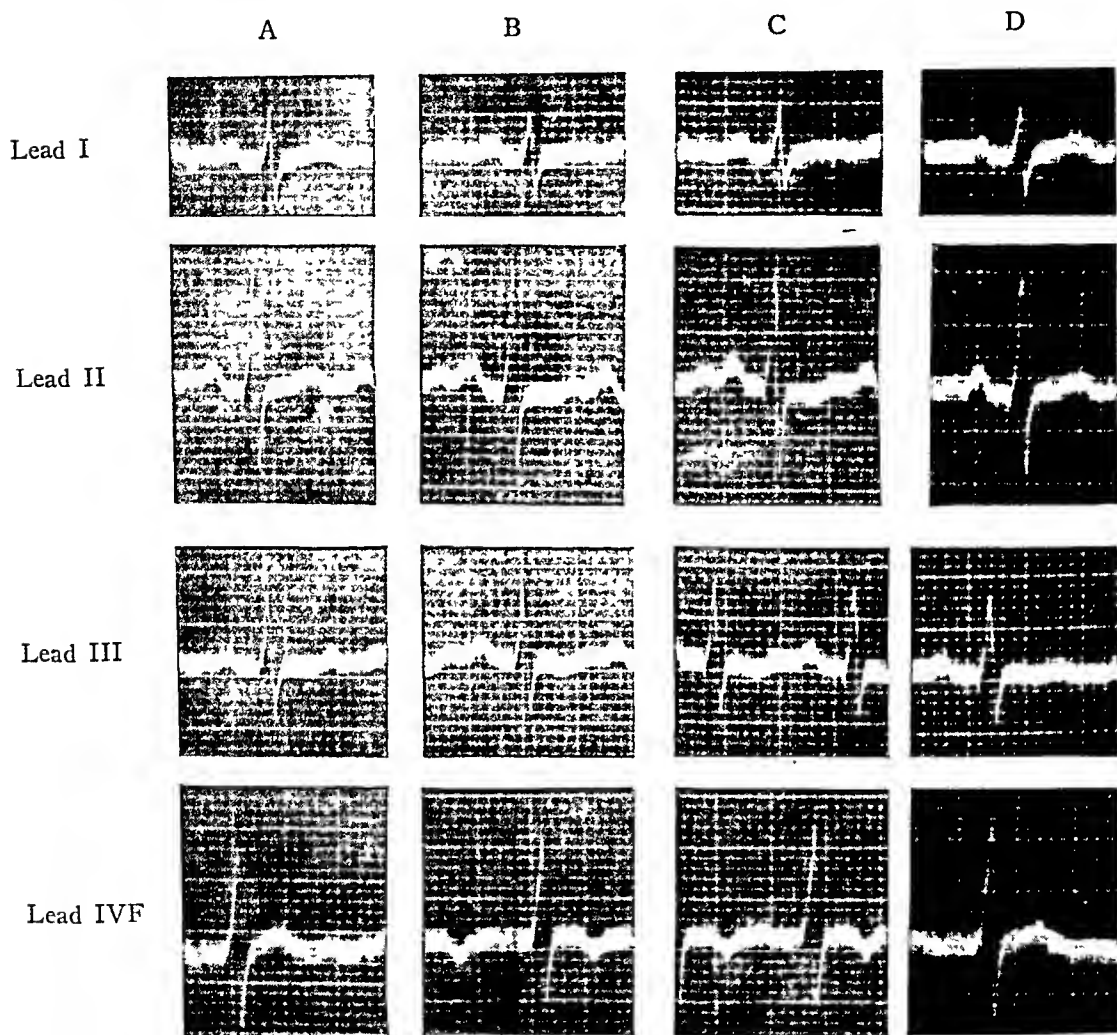


FIG. 4. Case 7 (Table 4). Age 32. No disease. A: Control record. B: After 10 minutes of anoxia. C: After 20 minutes of anoxia. D: After 100 per cent oxygen and room air. Criterion 3.

of the test before it was done, showed a negative objective test at 10 minutes and, having expressed increased dislike of the procedure, at 12 minutes ripped the mask from his face. He had no apparent discomfort beyond his fear reaction.

#### COMMENT

An attempt has been made to evaluate the anoxemia test for coronary insufficiency devised by Levy and his co-workers, as to its diagnostic efficacy

and its safety. Two hundred controls and 20 cases of definite coronary insufficiency were utilized. Electrocardiographic criteria No. 1, No. 2 and No. 3 were used, and the three precautions emphasized were followed.

It was not possible to use one cylinder of a 10 per cent  $O_2$ -90 per cent  $N_2$

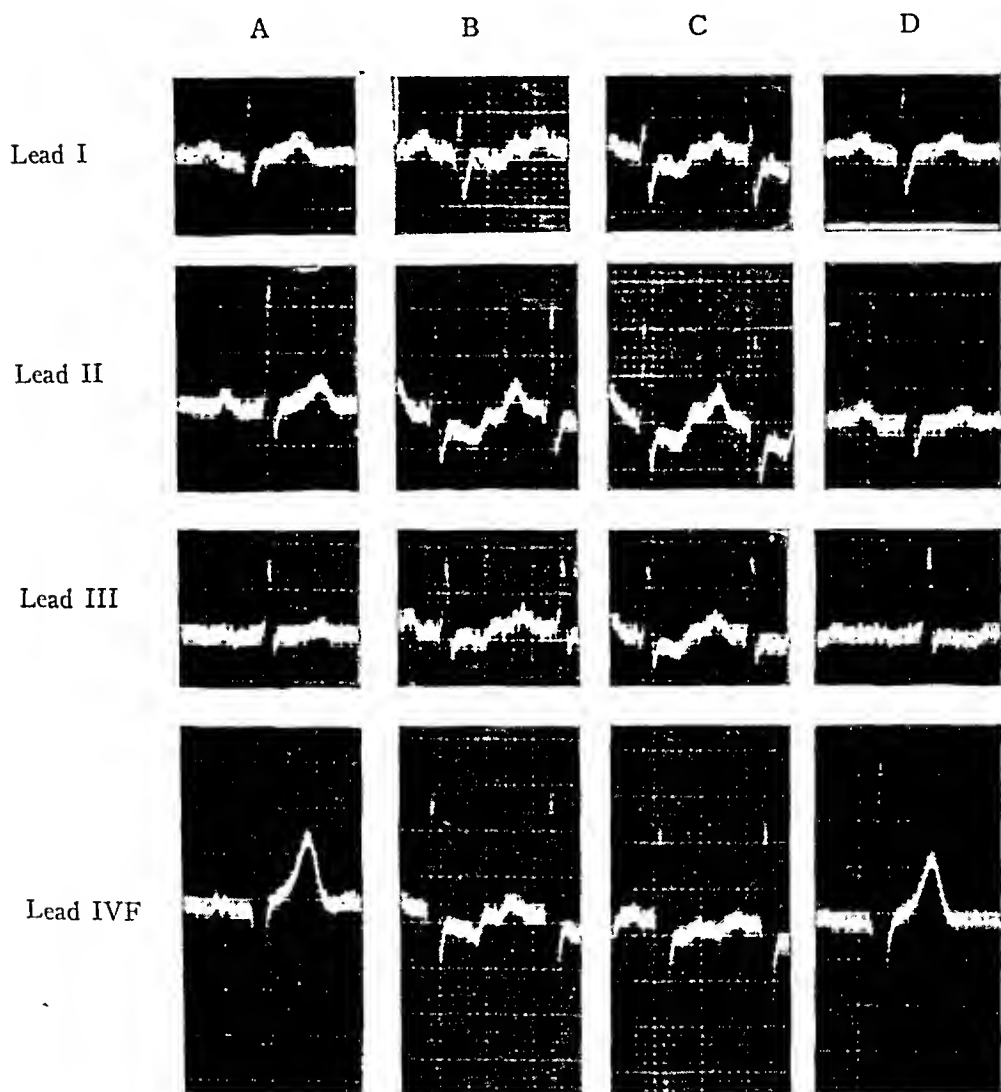


FIG. 5. *Case 2* (Table 4). Age 25. Malaria (chronic), hookworm infestation (chronic, persistent), anemia (secondary, marked). A: Control record. B: After 10 minutes of anoxia. C: After 20 minutes of anoxia. D: After 100 per cent oxygen and room air. Criteria 1 and 2.

mixture, nor to do gas analyses on the inspired mixture. The latter is particularly regretted.

The tests were done at approximately 700 feet above sea level, which we consider to be close enough to the level at which Levy's criteria for 10 per cent  $O_2$ -90 per cent  $N_2$  mixtures were established for us to use the same percentage mixtures without serious error.



The tests were all done at least two hours after meals. Gardberg and Olsen<sup>16</sup> demonstrated 30 to 50 per cent decrease in the height of T-waves in Leads I or III, or in all three limb leads. The maximum change was reported reached at one hour after food, persisted at this level for one and one-half to 2 hours, and then began to disappear.

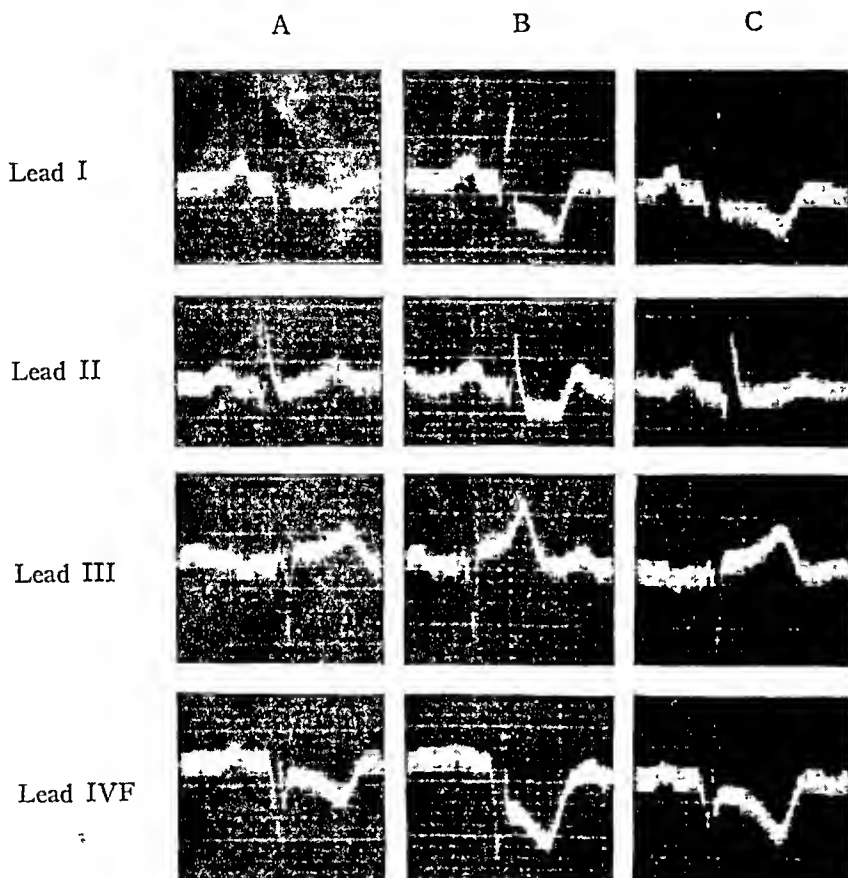


FIG. 6. Case 5 (Table 1). Age 63. Arteriosclerotic heart disease, one old infarction. A: Control record. B: Anginal pain after five minutes of anoxia. C: After 100 per cent oxygen and room air. Criteria 1 and 2.

We consider the test to be an office procedure, requiring a team of two, the doctor and the technician. Our procedure was comparable to that in an internist's office. If we disregard the two cases of coronary insufficiency where the test was continued beyond the onset of pain (and nitroglycerine and a short period of bed rest were required for complete recovery), not a single test required interruption due to serious or dangerous reaction, and not a single test required anything beyond the administration for one minute of 100 per cent O<sub>2</sub> for apparent complete recovery. As regards long-term effects we cannot say, except that we have observed several of our cases, from both series, for from several weeks to nine months, without evidence noted of apparent injurious effect. The physician was always present during the

test, and intermittently checked the patient's condition, but was generally busy at his desk in the same office while the test was being run. The technician, however, was in constant attendance upon the patient. The patient left immediately upon conclusion of the test.

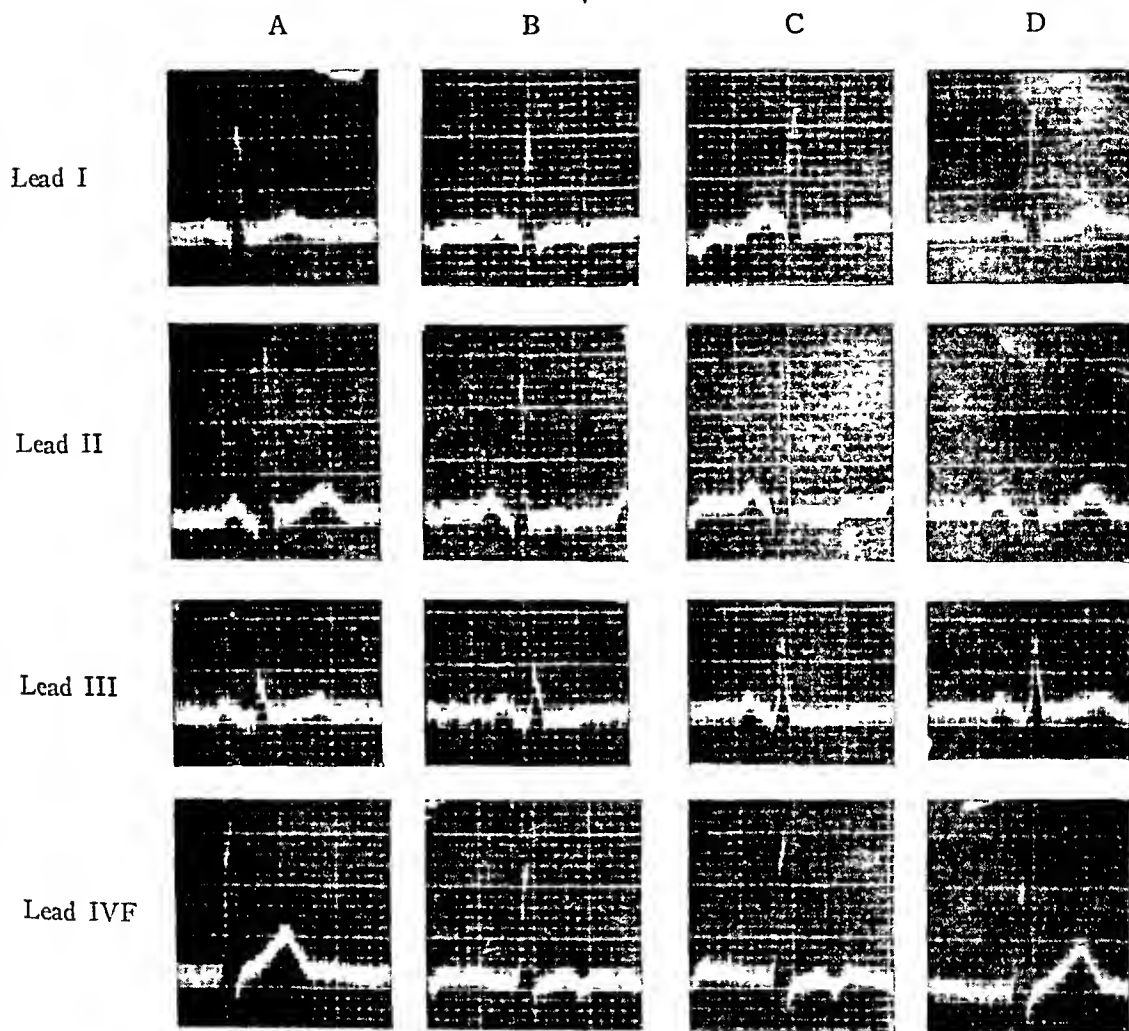


FIG. 7. Case 4 (Table 4). Age 37. Prominent left ventricle (fluoroscopy), low  $T_1$ , notched R. A: Control record. B: After 10 minutes of anoxia. C: After 20 minutes of anoxia. D: After 100 per cent oxygen and room air. Criteria 1 and 3.

We consider that if the three precautions noted earlier in the paper are observed, and if no test is continued beyond the onset of pain (there was always enough time to take a four-lead electrocardiogram before switching to 100 per cent  $O_2$ ), that the test is a safe procedure, in our experience.

The 20 cases of coronary insufficiency gave 11 (55.0 per cent) positive objective tests. In addition, seven (35.0 per cent) more gave positive presumptive tests, giving a total of 18 (90.0 per cent) positive tests, objective and/or presumptive. None of the 200 controls developed pain. Nine (4.5

per cent) gave positive objective tests. Four of these nine cases had abnormal cardiovascular factors present. One had a moderately severe anemia. One had had acute rheumatic polyarthritis four months previously, with the possibility of rheumatic coronary arteritis being present. One de-

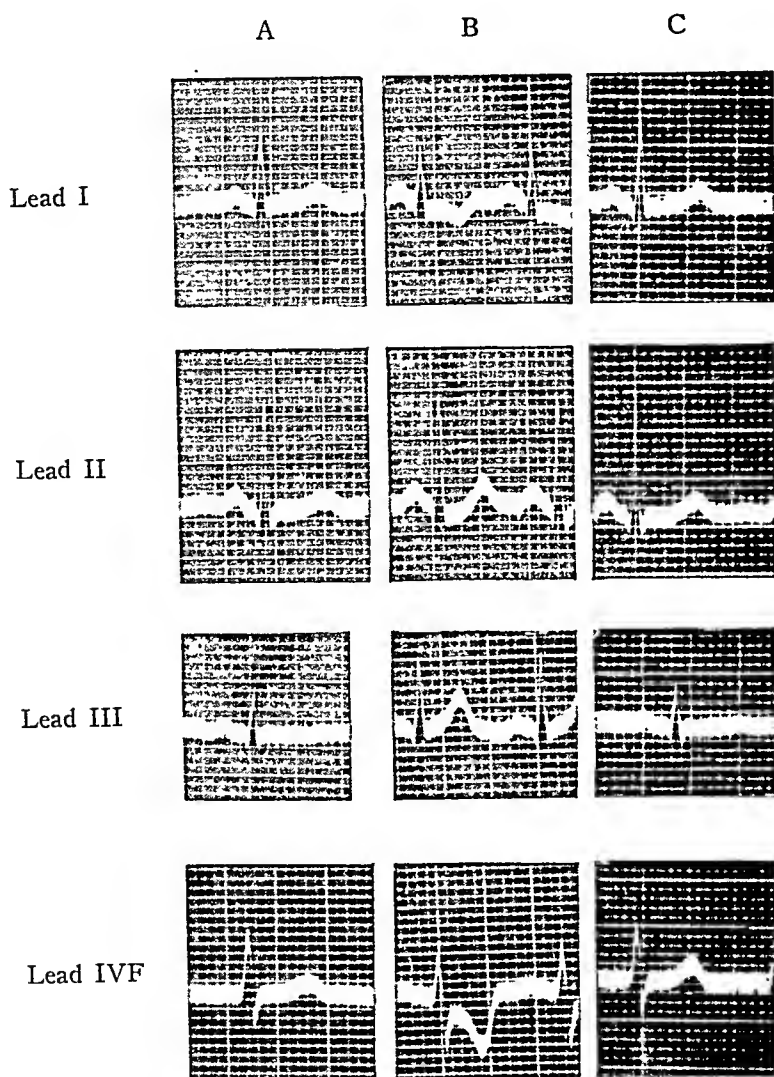


FIG. 8. Case 9 (Table 1). Age 49. Arteriosclerotic heart disease. A: Control record. B: Anginal pain after three minutes of anoxia. C: After 100 per cent oxygen and room air. Criteria 1, 2 and 3.

veloped an intense emotional reaction (fear) to the test. Mainzer and Krause<sup>17</sup> have shown that emotion, especially fear, may affect the form of the electrocardiogram, changes sometimes occurring in both T-waves and RS-T segments. In the last two of these nine we have decided that no cardiovascular, hemic or emotional factors were present, although one case (case 7, table 4) revealed sinus tachycardia, a slightly low T<sub>1</sub> and a low-normal T<sub>2</sub>. The other of these two (case 6, table 4) had been observed a

few days before the test to play continuously 36 holes of golf on a moderately hilly course, without the slightest symptomatic difficulty. These two cases (or 1.0 per cent of the control group) may be considered either as false positives, or as examples of coronary insufficiency of obscure etiology.

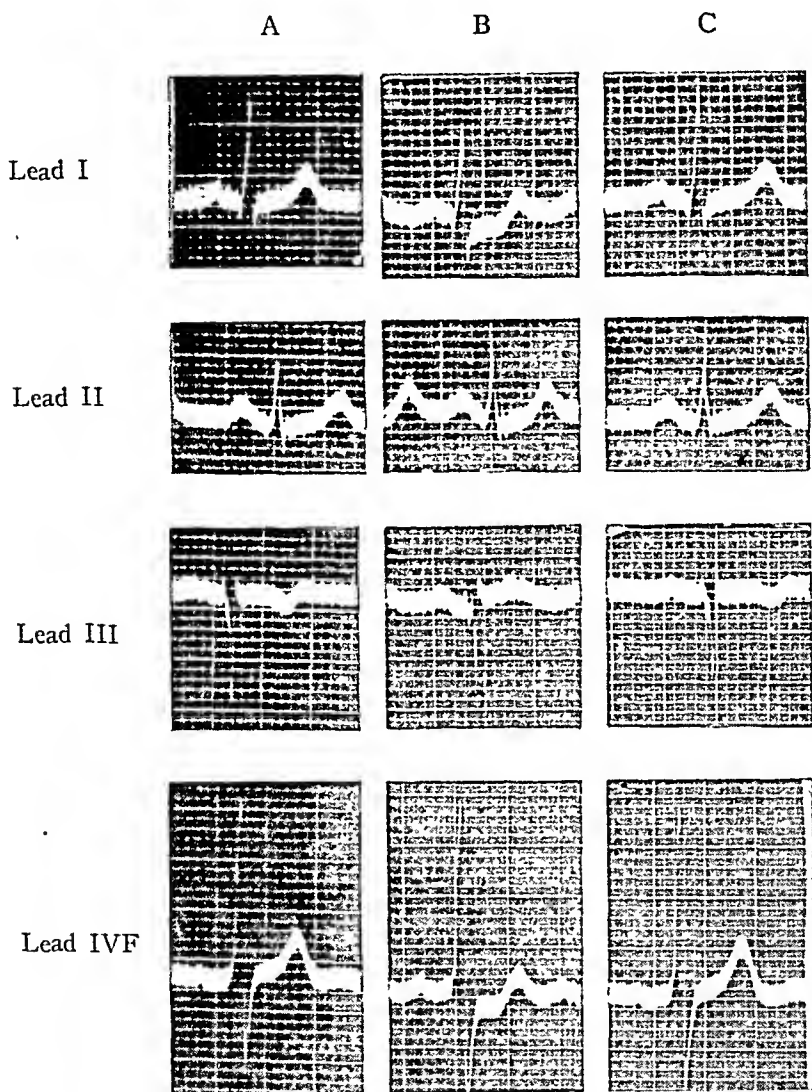


FIG. 9. Case 7 (Table 1). Age 39. Hypertensive and arteriosclerotic heart disease. A: Control record. B: Anginal pain after three and one-half minutes of anoxia. C: After 100 per cent oxygen and room air. Criterion 1.

Burnett et al.<sup>13</sup> found that 24 cases (19.2 per cent) of 125 normals gave positive tests, mostly inversion of  $T_1$  (criterion No. 3). They state that "reversal of T in Lead IVF (criterion No. 3) in response to induced anoxemia cannot be accepted as indicative of coronary insufficiency." Patterson, Clark and Levy,<sup>8</sup> on the other hand, observe that "in not a single normal person (136 cases) was the direction of T in IVF completely reversed, whereas in the coronary patients (157 cases) this was noted in 23 tests."

We found criterion No. 3 present in four cases, but in only one case was it present alone. That was case 7 (table 4) of the control group, which was one of the two cases which may be considered as false positives or as cases of coronary insufficiency of obscure etiology. We can draw no conclusion,

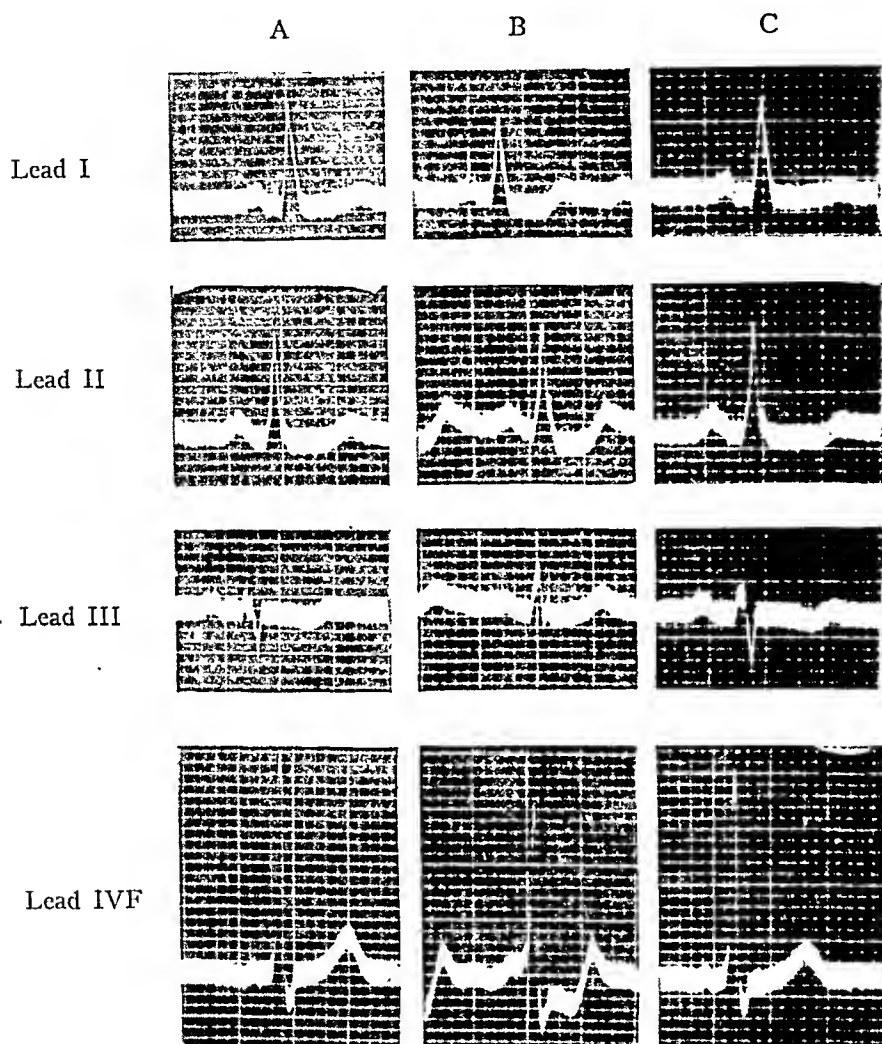


FIG. 10. Case 1 (Table 1). Age 54. Hypertensive and arteriosclerotic heart disease, two old infarctions. A: Control record. B: Anginal pain after four minutes of anoxia. C: After 100 per cent oxygen and room air. Criterion 1.

obviously, from our work concerning the diagnostic usefulness of criterion No. 3.

It must be remembered, as stated by Levy and his co-workers, that a negative electrocardiographic test does not rule out coronary insufficiency, and that the development of pain, particularly within the first 10 minutes of anoxia, affords only *presumptive* evidence of diminished coronary reserve.

Realizing that the judgment of the clinician is of paramount importance in the making of a diagnosis of coronary insufficiency, we consider that a test

such as this, which gives 55.0 per cent objective confirmation in diagnosed known cases of coronary insufficiency, and only 1.0 per cent false positives in controls, may be used as a valuable aid, in careful hands, in the making of the diagnosis of coronary insufficiency.

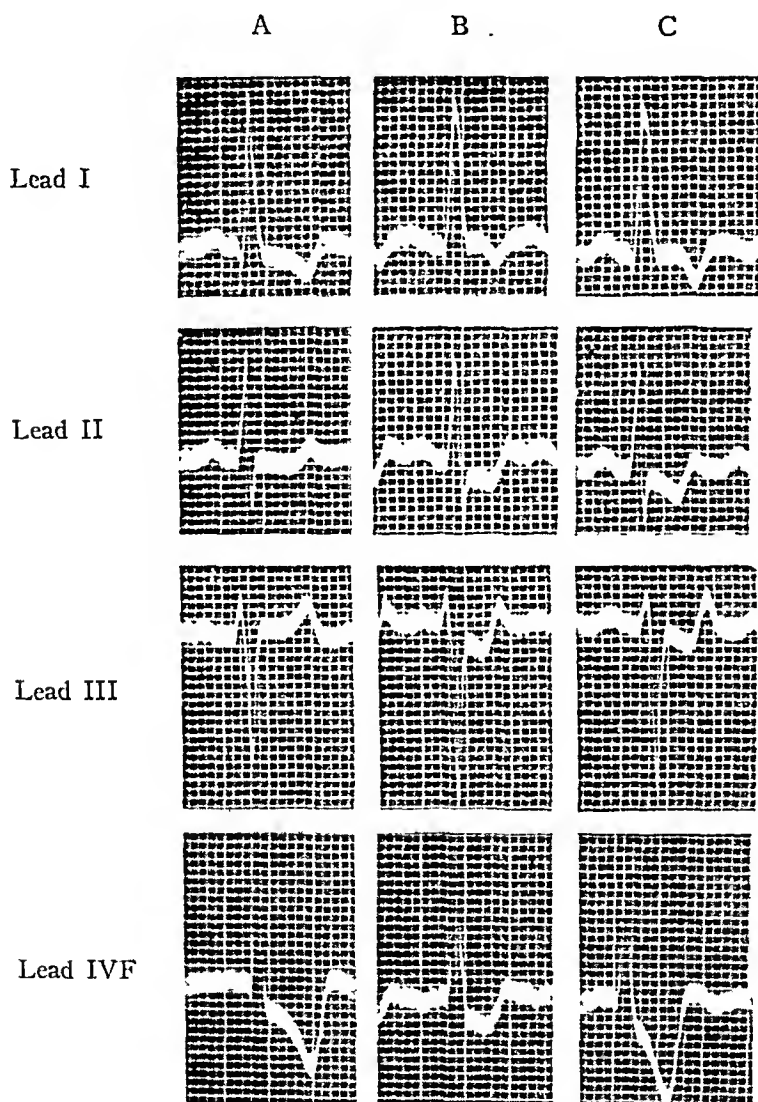


FIG. 11. Case 10 (Table 1). Age 58. Rheumatic and arteriosclerotic heart disease. A: Control record. B: Anginal pain after three and one-half minutes of anoxia. C: After 100 per cent oxygen and room air. Criterion 1.

#### SUMMARY AND CONCLUSIONS

1. An evaluation as to diagnostic efficacy and as to safety has been attempted of the anoxemia test for coronary insufficiency (as standardized by Levy and his co-workers), with 200 controls and 20 cases of coronary insufficiency.

2. Fifty-five per cent (11 cases) of the 20 cases of coronary insufficiency gave positive objective (electrocardiographic) tests. In addition, 35.0 per

cent (seven cases) more gave positive presumptive tests, giving a total of 90.0 per cent (18 cases) positive tests, objective and/or presumptive.

3. Four and five-tenths per cent (nine cases) of the 200 controls gave positive objective tests. There were no positive presumptive tests in the control group.

4. Of this 4.5 per cent (nine cases), there were only two cases (1.0 per cent of the control group of 200) which had no abnormal cardiovascular, hemic or emotional factors present which might account for a positive test.

5. This 1.0 per cent may be considered either as false positives, or as examples of coronary insufficiency of obscure etiology.

6. Within strict limits (as defined by Levy and his co-workers); and with the added caution that the test shall be terminated immediately after a four-lead electrocardiogram taken directly at the onset of pain, we consider that this test is safe, is an office procedure, and requires the attendance of the physician and one technician. Reactions are readily relieved by the administration of 100 per cent O<sub>2</sub>.

7. Using the interpretations of the test as stated by Levy and his co-workers, we consider that this test is a valuable aid in the making of the diagnosis of coronary insufficiency.

Appreciation is expressed for the excellent technical assistance of Mr. Louis Wright, Mrs. Mattie F. Hinton, and Mrs. Claudia S. Beaulieu.

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# CASE REPORTS

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## XANTHOMATOUS BILIARY CIRRHOSIS: LIPID LEVELS WHILE RECEIVING INOSITOL \*

By MAURICE C. GEPHARDT, M.D., *Chicago, Illinois*

VARIOUS studies of the lipotropic action of inositol in experimental animals have been reported. The present case was studied to observe the results of inositol on an extreme hyperlipemia in the human being.

### CASE REPORT

A 37 year old, unmarried, Jewish woman was admitted to the Illinois Research and Educational Hospital on August 9, 1944. In 1942 she had first noted itching of the palms which was followed by the appearance of pale yellow lesions of the skin along the palmar folds. Yellow, non-inflammatory nodules later appeared over the knuckles, over the olecranon processes, along the creases over the cubital fossae, over the patellae, superficial to both Achilles' tendons, and over some of the joints of the toes. More recently less elevated infiltrations had appeared in the skin of the forehead, eyelids, and trunk. After March 1944 the patient had an increased generalized pruritus. She suffered sufficient fatigability and weakness to interfere with her housekeeping. She had weighed 150 pounds most of her adult life, but lost 25 pounds during the year before admission. The patient stated that she had lost her appetite and suffered from insomnia. During the early part of August, 1944 she first noted slight pain in the right upper quadrant with no radiations.

The patient worked in her father's grocery store and ate whatever and whenever she liked. There was no family history of a similar illness nor of diabetes mellitus. Several months before the appearance of the skin lesions she had taken 15 mg. of thiamine chloride daily for eight weeks. This was discontinued because of a gain in weight and increased appetite.

At the time of admission she had a normal temperature, pulse, respiratory rate, and blood pressure. She weighed 98 pounds. There were extensive cutaneous infiltrations as raised yellow nodules on the extensor prominences and at the sites of pressure and involving, especially, the hands, elbows, knees, and heels (figure 1). A flat, linear yellow type of lesion was present along the flexor folds of the hands and fingers (figure 2), at the corners of the mouth, and along the folds over the cubital fossae. In the skin of the forehead, trunk, and eyelids there were flat yellow infiltrations of irregular outline (figure 3). The eyelashes were sparse, sclerae were icteric, and conjunctivae were injected. Corneal opacities prevented visualization of the fundi. An internal strabismus of the left eye was present. The teeth were in poor repair. The diaphragm was elevated but moved freely on both sides. Heart and lung findings were normal. The liver margin was 4 cm. below the costal margin in the right anterior axillary line. It was smooth and non-tender. The spleen was barely palpable. Pelvic and neuro-muscular findings were normal.

Laboratory findings were as follows:

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From the Department of Medicine, College of Medicine, University of Illinois.

Red blood cells.....	3,500,000
Hematocrit.....	36 mm.
Hemoglobin.....	9.5 gm.
White blood cells.....	5,000
Differential.....	Normal
Sedimentation rate.....	Normal
Urine.....	Normal
Exton-Rose glucose tolerance	
fasting.....	97 mg. per cent
one-half hour.....	116 mg. per cent
one hour.....	80 mg. per cent
Non-protein nitrogen.....	36.3 mg. per cent
Urea nitrogen.....	16.8 mg. per cent
Icterus index.....	39
Serum bilirubin.....	5.5 mg. per cent
Serum albumin.....	4.1 mg. per cent
Serum globulin.....	3.4 mg. per cent
Total cholesterol.....	1193 mg. per cent
Cholesterol esters.....	254 mg. per cent
Wassermann and Kahn tests.....	Negative
Electrocardiogram.....	Normal
Basal metabolic rate.....	+28 per cent
Prothrombin time.....	Normal
(Kato-Poncher technic)	
Hippuric acid liver function test.....	Normal

The basal metabolic rate was confirmed by respiratory quotient studies in which the oxygen consumption per square meter per hour indicated a utilization of 44.4 calories as compared to 35.7 calories, the normal for this patient. Biopsy of a skin lesion confirmed the dermatological diagnosis of xanthoma tuberosum multiplex. Several attempts to perform a bromsulfalein excretion test were unsuccessful because the serum would gel immediately upon addition of the sodium hydroxide.

Roentgenologic studies of the chest revealed elevation of the diaphragm and an old healed hilar tuberculosis with no recent or active lesion. The skull films were negative. The gall-bladder visualization with Dikol showed poor concentration but the gall-bladder contracted and no gallstones could be demonstrated.

Thannhauser's triad for the diagnosis of xanthomatous biliary cirrhosis are: (1) jaundice of several years' duration, (2) enlarged liver and spleen, and (3) hypercholesterolemia without a milky serum.<sup>1</sup> Our case fulfilled all of these criteria. Treatment was started with a low fat, low cholesterol diet of 1616 calories consisting of 240 gm. of carbohydrate, 102 gm. of protein, and 28 gm. of fat. This was continued until December 12, 1944. Because the patient was losing weight the diet was changed to 302 gm. of carbohydrate, 89 gm. of protein, and 27 gm. of fat, yielding 1807 calories. After the initial fat determination on September 16, 1944, the patient received 1.5 gm. of choline hydrochloride daily in divided doses until October 18, 1944. On this date all medications were discontinued until December 4, 1944 when administration of 3.0 gm. of inositol daily in divided doses was begun. This medication and diet were the only therapy employed from that date until February 17, 1945 when 4.5 gm. of choline daily were added. Throughout June 1945 she also received methionine in doses of 0.9 gm. daily.



FIG. 1. Xanthomatous nodules over the Achilles' tendons.

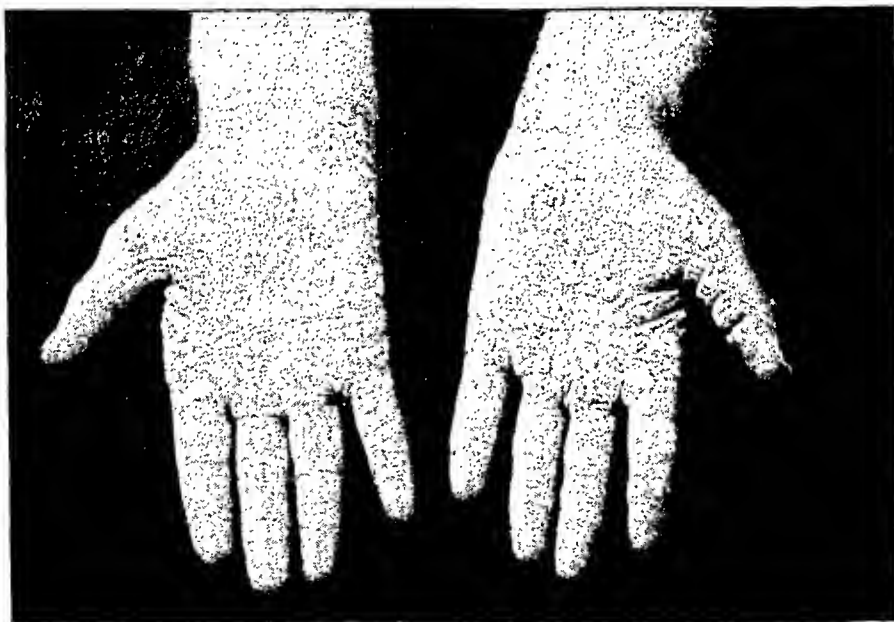


FIG. 2. Flat, linear xanthomatous lesions along the flexor folds of the hands and fingers.

Blood lipid studies were started September 16, 1944 and specimens were taken at intervals through June 29, 1945. All lipid determinations were taken on fasting blood specimens drawn in the morning using heparin as the anti-coagulant. The plasma values of total lipid carbon, of phosphorus of the phospholipids, of cholesterol in both total and free cholesterol were determined. They served as the data for calculating the total lipid, total cholesterol, free cholesterol, cholesterol esters, and neutral fat by the methods of Page, et al.<sup>2</sup>

The total carbon, phosphorus, and free cholesterol were determined from a petroleum ether extract prepared from Bloor's alcohol-ether extract. Van Slyke and Folch<sup>3</sup> give the technic for preparing the petroleum ether extract and the method of determining the total carbon. For the total cholesterol determination a specimen of Bloor's alcohol-ether extract was hydrolyzed while alkaline and a



FIG. 3. Xanthomatous lesions of the forehead, eyelids and about the mouth.

petroleum ether extract was made after acidification. The cholesterol in the specimens for both free and total cholesterol was precipitated as the digitonides, washed,<sup>4</sup> and dried. Glacial acetic acid was used for decomposition and the color developed with acetic anhydride and sulfuric acid.<sup>5</sup> The phosphorus content of the petroleum ether extract was determined by a method devised by Dr. A. B. Kendrick in which the ether is boiled off in the presence of water, the organic matter is oxidized with sulfuric acid and potassium permanganate, the solution is cleared of manganese dioxide with oxalic acid, and the color change is produced with stannous chloride. The color intensities were measured photometrically in the phosphorus and cholesterol reactions.

Page et al.<sup>2</sup> pointed out that abnormal blood lipid levels are often associated with altered ratios of the various fat components. Hence, it is no surprise that a more accurate total lipid value was obtained in this patient by summation of the components than by taking the product of the total carbon and 1.30, the usual constant. The following table illustrates this.

TABLE I

	Normal	Patient's values Sept. 16, 1944
Total Lipid by		
(a) total carbon $\times$ 1.30	735.4 mg. %	4499.1 mg. %
(b) summation	737.6 mg. %	4896.8 mg. %
Per cent composition		
Phospholipid	24.53%	58.29%
Total cholesterol	31.45%	28.59%
Cholesterol ester	33.22%	7.86%
Free cholesterol	11.12%	23.84%
Neutral fat	31.14%	10.01%

The accompanying graph presents the results obtained from our studies (figure 4).

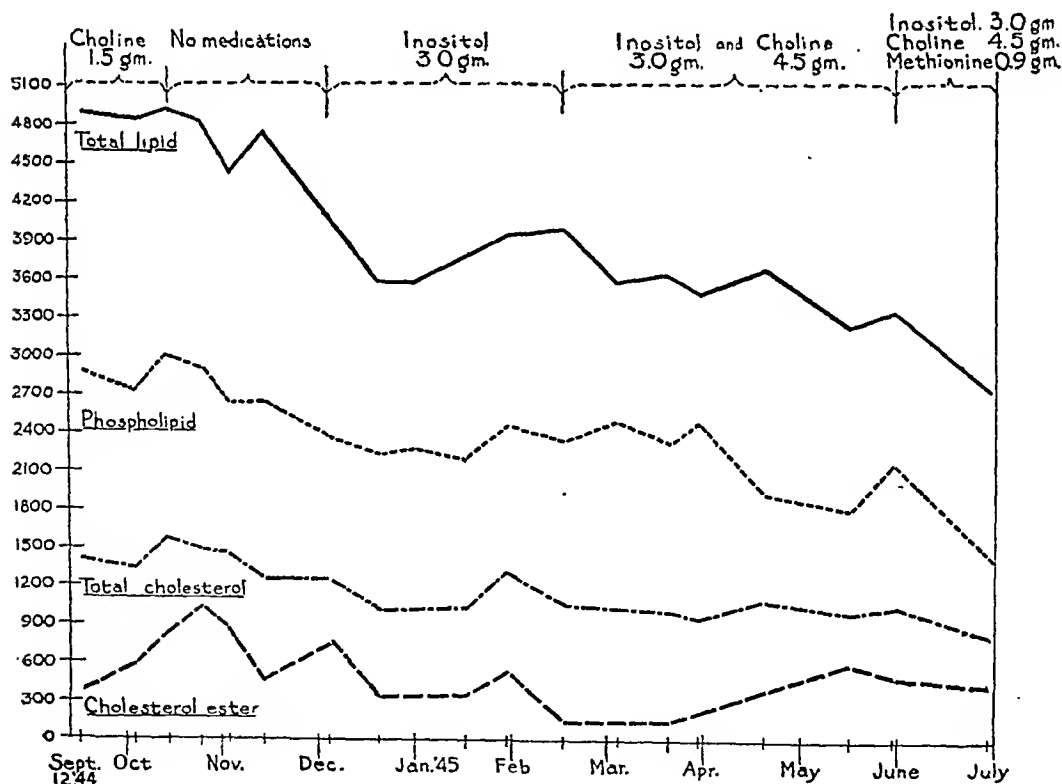


FIG. 4.

The patient's hospital course was not remarkable until June 28, 1945. In the evening of this day she developed a sudden elevation of temperature to 104° F.<sup>6</sup> The blood specimen for June 29, 1945 was taken 16 hours after the onset of this fever. The patient was remarkably asymptomatic despite the increased

temperature. Its etiology remains undetermined. No conspicuous change occurred in the skin lesions during the period of study. While the patient was under treatment she developed a small vascular area in the right cornea which was the site of a slow deposition of an opaque material resembling the xanthomatous material deposited in the skin. On July 20, 1945 she had a serum bilirubin of 5.8 mg. per cent and icterus index of 37.

Our results in this case suggest that: (1) A lowering of the blood lipid level was produced with diet and inositol; (2) choline may have aided in further depressing the lipid level; (3) prolonged studies are necessary to evaluate any lipotropic activity; and (4) the serum bilirubin and icterus index values were independent of the lipid levels.

My sincerest gratitude is due Dr. Robert W. Keeton for his suggestions in the clinical problems and Dr. A. B. Kendrick for his technical guidance.

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#### PAROXYSMAL VENTRICULAR TACHYCARDIA WITH ACUTE LEFT VENTRICULAR FAILURE IN A PATIENT WITH NO EVIDENCE OF ORGANIC HEART DISEASE\*

By MAX H. STEIN, Captain, M.C., AUS, *Brooklyn, N. Y.*, and ROBERT E. DRISCOLL, Captain, M.C., AUS, F.A.C.P., *Chicago, Illinois*

THE association of paroxysmal ventricular tachycardia with acute left ventricular failure and pulmonary edema in an individual with no demonstrable organic heart disease is a rarity. Such experience with a young soldier is therefore reported.

#### CASE REPORT

A soldier, (white) age 18, with 10 months of military service, was admitted to the hospital at 7:30 p.m., January 16, 1946, because of a sudden onset of cardiac palpitation, chest pain and moderate dyspnea. The patient had been imbibing freely of alcohol during the day and about one half hour prior to admission he noted the above symptoms, for which he voluntarily sought hospitalization.

\* Received for publication April 30, 1946.

From Medical Service, ASF Regional Station Hospital, Fort Leonard Wood, Missouri.

Family History: Non-contributory.

Past History: He gave a history that since the age of five he had had recurrent attacks of cardiac palpitation of sudden onset associated with shortness of breath and cough. In the past these spells had lasted from 10 minutes to 10 hours and usually subsided spontaneously, but occasionally would be stopped by vomiting. He had never had any specific therapy.

Physical Examination on Admission: He was a well-developed, robust, white male, who was very boisterous and difficult to control because of his alcoholic intoxication. He was moderately dyspneic, but not cyanotic. The lung fields were

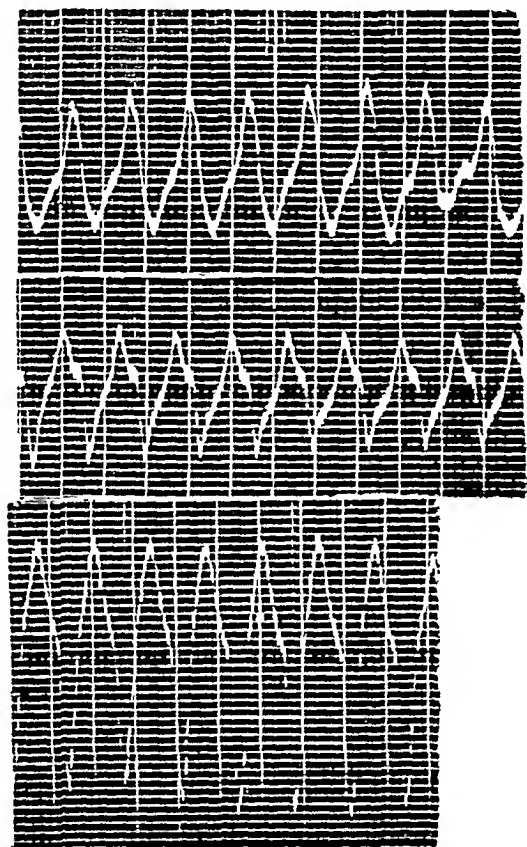


FIG. 1. Paroxysmal ventricular tachycardia, January 16, 1946, evening of admission, rate 230 per minute.

clear. The cardiac rate was counted as 200 per minute and the rhythm was regular. The blood pressure was 90 mm. Hg systolic and 60 diastolic. Abdominal examination was negative and there was no evidence of any peripheral edema.

The patient was given paraldehyde (5 c.c. intramuscularly) and seconal (1½ grains orally) for sedation.

Course in Hospital: The patient was fairly comfortable until about 8:30 p.m. (one hour after admission) when he suddenly developed severe dyspnea, orthopnea, cyanosis, and cough with expectoration of large amounts of bloody, frothy sputum. The cardiac rhythm at this time was slightly irregular, which was most apparent at the radial pulse. The rate was now too rapid to count. The lungs on physical examination presented the classical signs of pulmonary edema. The liver was not palpably enlarged and there was no demonstrable peripheral edema.

Because of the urgency of the situation, treatment for the pulmonary edema was instituted before an electrocardiographic tracing was made. He was given morphine sulfate ( $\frac{1}{2}$  grain subcutaneously) and 5 ampules of digifoline (5 cat units) intravenously, after the removal of 400 c.c. of blood by phlebotomy. He was also given oxygen therapy by B.L.B. mask.

Immediately after the above measures, an electrocardiogram was taken, and the arrhythmia which had been present since admission (about one hour before), was shown to be a paroxysmal ventricular tachycardia with a rate of 230 per minute (figure 1).

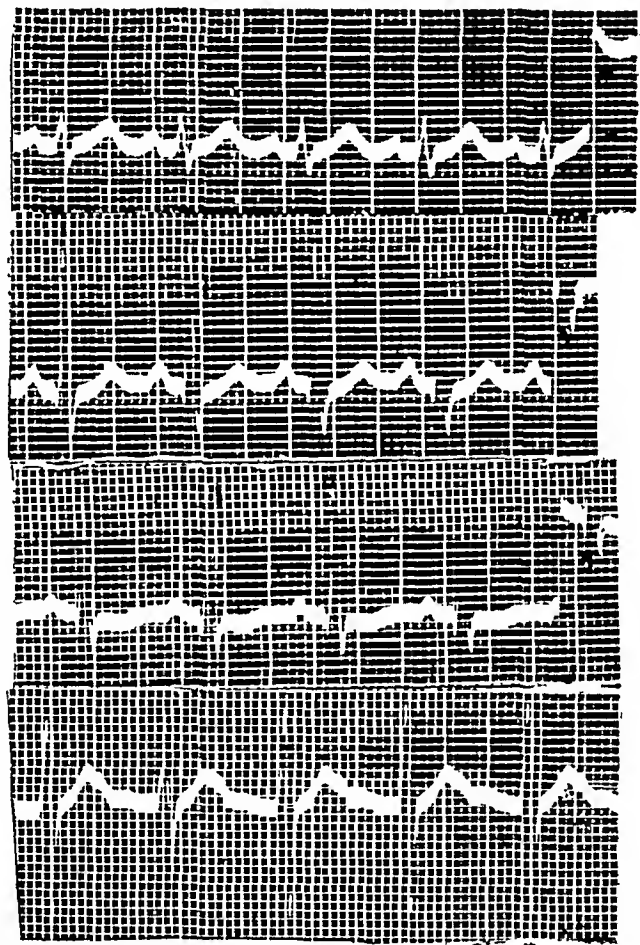


FIG. 2. January 17, 1946, rate 110, three hours after cessation of the attack of ventricular tachycardia.

Carotid sinus pressure, the Valsalva experiment and all other methods usually employed for supra-ventricular paroxysmal tachycardias failed to affect this patient. He was then given 3 grains of quinidine sulfate by mouth as a test dose, which was then followed by 5 grains every three hours. After the oral administration of 13 grains of quinidine sulfate the patient experienced a cessation of his cardiac palpitation and a regular sinus rhythm was restored. An electrocardiogram taken about three hours after the cessation of the paroxysm showed a sinus tachycardia with a rate of 110 per minute (figure 2).

Before quinidine therapy could be effective and within a few minutes after the emergency measures were started, the pulmonary edema began to subside and the patient's general condition improved.



Twelve hours after admission the patient was comfortable, breathing normally and had no evidence of pulmonary congestion on physical examination. The only abnormal finding was a sinus tachycardia as indicated in the electrocardiogram (figure 2). The blood pressure was now 120 systolic and 80 diastolic and no cardiac murmurs or any other adventitious heart sounds could be heard. Within the next 24 hours the cardiac rate was 80 to 90 per minute and of a regular sinus mechanism, shown by electrocardiogram (figure 3).

During the next few days he was normal in every respect, both in bed and as an ambulatory patient. Heart fluoroscopy and roentgenogram were normal. All other laboratory studies, including basal metabolic rate, blood count, urine, blood sedimentation rate, and blood Kahn were normal. Repeated clinical examinations of the heart were normal and failed to indicate any form of organic heart disease.

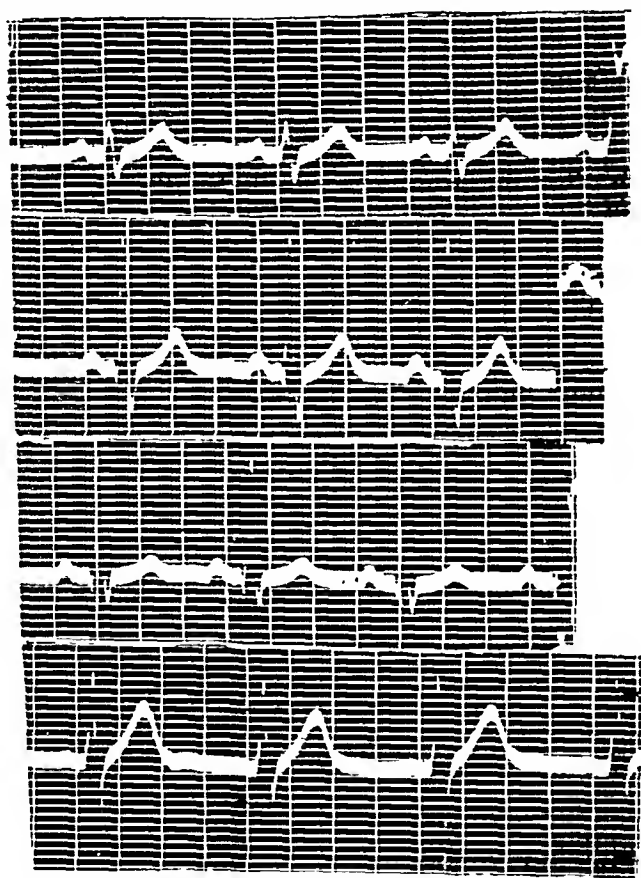


FIG. 3. Regular sinus rhythm, January 18, 1946, rate 80.

#### DISCUSSION

That paroxysmal ventricular tachycardia may occur in persons without organic heart disease is not generally recognized, although several instances have been reported.<sup>1, 2, 3, 4</sup>

In one of the largest series of cases of ventricular tachycardia, reported from one hospital, Williams and Ellis found that 35 out of the 36 cases with this arrhythmia had underlying organic heart disease.<sup>2</sup>

In the presence of organic heart disease, ventricular tachycardia is of grave prognostic significance. With no organic heart disease present the paroxysms

are usually not of grave significance and revert to a regular sinus rhythm either spontaneously or with quinidine therapy. Nevertheless, paroxysmal ventricular tachycardia is always more serious than the usually innocent supra-ventricular tachycardias. A fatal termination of an attack of paroxysmal ventricular tachycardia in a 19 year old patient with no evident organic heart disease was reported by Elliott and Fenn.<sup>3</sup> Death in this case was due to congestive heart failure resulting from the paroxysm lasting 32 days and not responding to treatment.

The case reported in this communication is of interest for two reasons, namely:

1. The paroxysmal ventricular tachycardia occurred in an 18 year old soldier with no evidence of organic heart disease.

2. One and one half hours after the onset of the arrhythmia, acute left ventricular failure with pulmonary edema followed.

It is well known that tachycardia of any type may produce congestive heart failure in a person with organic heart disease. In their series of 36 cases, Williams and Ellis found that 86 per cent of the patients showed evidence of congestive heart failure, in association with their ventricular tachycardia.<sup>2</sup> However, in no patient could it be shown that the ventricular tachycardia preceded the congestive failure, but in two of the patients the heart failure was definitely aggravated by the tachycardia.

The sequence of events observed in the patient here reported, makes it evident that the paroxysm of ventricular tachycardia was the precipitating factor in the production of left ventricular failure with pulmonary edema. It is also probable that the alcoholic intoxication was responsible for the onset of the paroxysmal arrhythmia.

We are cognizant of the fact that digitalis may cause ventricular tachycardia to change to ventricular fibrillation, but because of the acuteness of the onset and severity of the pulmonary edema it was felt justifiable to use it. The cessation of the attack after 13 grains of quinidine sulfate were given orally cannot be definitely attributed to the quinidine. It is possible that the arrhythmia terminated itself spontaneously, as it had done in the many episodes in previous years, as related by the patient.

### SUMMARY

A case is presented of paroxysmal ventricular tachycardia with acute left ventricular failure and pulmonary edema, occurring in a young individual with no demonstrable organic heart disease, and followed by complete recovery.

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## THE ANTISTREPTOLYSIN TITER AS A DIAGNOSTIC AID IN CARDITIS OF OBSCURE ETIOLOGY \*

By NORMAN REITMAN, M.D., *New Brunswick, New Jersey*

FOR many years it has been recognized that hemolytic streptococcus infections may cause secondary cardiac changes varying from endocarditis and subsequent valvular deformities to a diffuse pancarditis, or simply a transient involvement of the conduction system.

When there is an accompanying migratory polyarthrititis, epistaxis, erythema marginatum or nodosum, or vague abdominal pain, the cardiac changes are said to be part of the symptom complex we recognize as rheumatic fever. However, when the pathologic change occurs in the conduction system alone, it is often difficult to prove that the cause is acute rheumatic fever; but on occasion the etiologic agent causing the cardiac changes can be traced by means of study of the immune bodies of the blood serum.

Todd<sup>1</sup> in 1932 showed that streptococcus hemolysin was capable of stimulating an antigenic response. He also showed that this antistreptolysin response was present in all types of clinical hemolytic streptococcus infections—erysipelas, scarlet fever, acute follicular tonsillitis, and rheumatic fever. There was no response noted in cases of rheumatoid or gonococcal arthritis. Todd<sup>2</sup> further showed that this immunological response remained for months following acute hemolytic streptococcus infections and was also present in the blood of individuals without clinical evidence or history of infection with the hemolytic streptococcus. However, in an acute infection there is a rising titer of antibodies from week to week which aids in differentiating an active from a quiescent process. This work has been substantially corroborated by Myers and Keefer.<sup>3</sup>

Although this diagnostic procedure has been known for some time, its use has been limited largely to research studies in experimental hemolytic streptococcus infections. In the case reported below the study of the antistreptolysin titer was found to be the only method of establishing the etiology of the carditis, and it is presented to stress the value of this important diagnostic aid.

### CASE REPORT

A white school boy, aged 15, was first seen on April 28, 1941, because of fever and headache. Two days prior, upon awakening, he felt nauseated, vomited once and thereafter felt better. The following afternoon the patient noticed a dull headache, felt tired and chilly but had no fever. The next morning he felt well enough to go to school and played baseball in the afternoon. That evening he again complained of a dull headache and chilly sensations. He was found to have a fever and a physician was summoned.

On examination, the patient did not appear ill. His temperature was 102.3° F., pulse rate 110, blood pressure 116 mm. Hg systolic and 72 diastolic. Physical findings were limited to the heart which was not enlarged, but a harsh systolic murmur could be heard at the mitral and aortic areas. The second pulmonic sound was accentuated. The quality of the heart sounds was good; no gallop, rub, or thrill was demonstrated. No murmurs had been heard on previous examination, and it was felt that the present mitral and aortic murmurs were due to the fever alone and symptomatic treatment was instituted.

\* Received for publication October 22, 1945.

The next morning the patient felt entirely well. No headache or malaise remained. There were no joint pains, epistaxis, rash or abdominal pain. His temperature was normal and he was eager to go to school.

Examination at this time revealed considerable change although findings again were limited to the heart. The heart sounds had become very poor in quality. The systolic murmur had disappeared, but the slapping second pulmonic sound remained. The cardiac rhythm was irregular, with a ventricular rate of 84 and a pulse rate of 76. No further symptoms or signs could be elicited. Laboratory findings: White

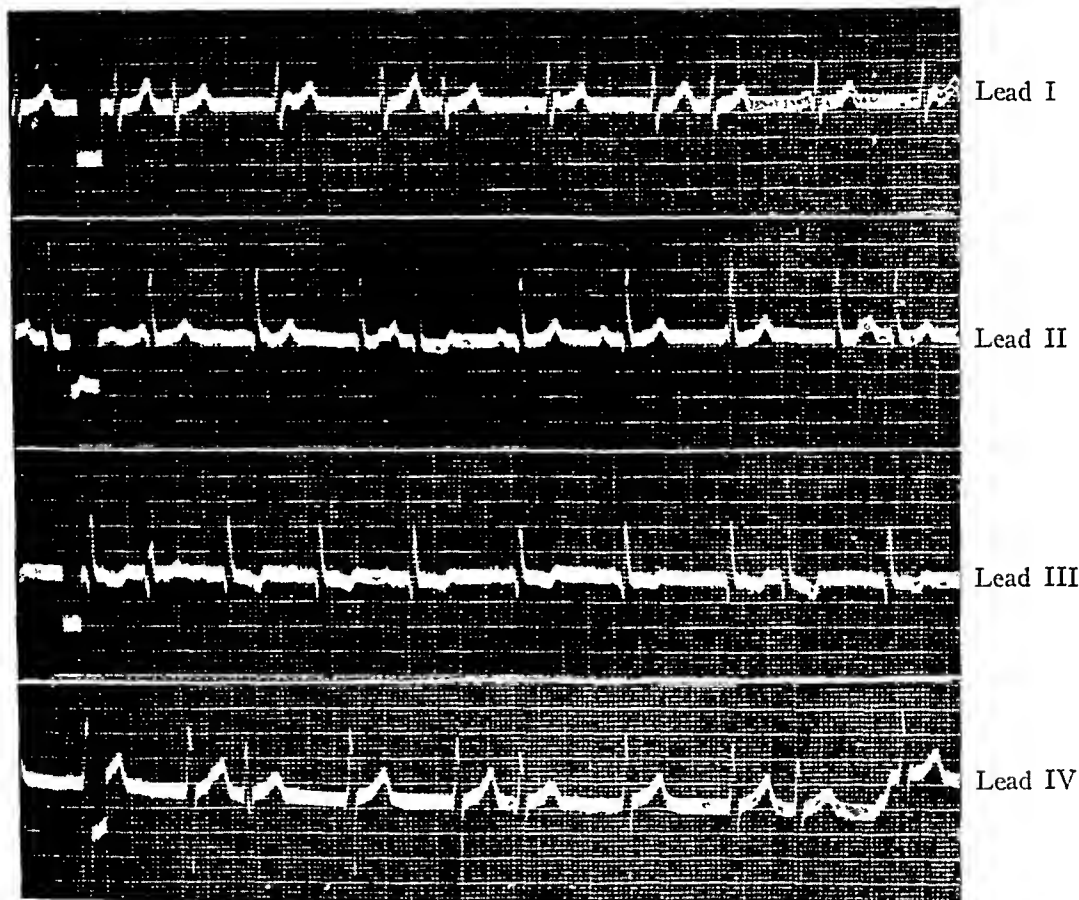


FIG. 1. Electrocardiograms, April 29, 1941.

blood cell count was 12,750; polymorphonuclears 78 per cent; lymphocytes 18 per cent; mononuclears 2 per cent; eosinophiles 2 per cent. Urine: acid; sp. gr. 1.018; albumin, 0; sugar, 0; microscopic, negative. The blood sedimentation rate was 76 mm. per hour (Westergren).

An electrocardiogram (figure 1) was bizarre. At first it was felt that we were dealing with a form of complete auriculo-ventricular dissociation, but on careful examination of the records it is seen that the essential rhythm is a slow sinus arrhythmia with ventricular escape. This is most evident in Lead II, where there is a definite sequence between the P-wave and QRS group in the sixth and seventh complexes, followed by several escaped ventricular beats in which the P-wave is not evident, being included in the QRS complexes.

Because of these findings a diagnosis of acute carditis, of undetermined etiology, was made. The patient was placed on a régime of strict bed rest and sodium salicylate gm. 1.0 q.i.d.

On May 2, the heart sounds had become progressively weaker, and the systolic murmur had reappeared. The ventricular rate was 56 per minute, pulse rate 62 per minute. There still were no subjective complaints. An electrocardiogram taken on May 2, 1941 (figure 2) revealed a definite change from the preceding one. There was a regular sinus bradycardia. The P-R interval was slightly prolonged for a 15-year old boy (0.20–0.21 sec.), and the T-waves in Leads II and III were of



FIG. 2. Electrocardiograms, May 2, 1941.

much higher voltage. Another tracing on May 16, 1941 (figure 3) showed a decrease in the P-R interval to 0.16 sec. (It has remained at that level ever since.) Otherwise there were no significant electrocardiographic changes.

Clinically the patient remained afebrile and asymptomatic, and it was with difficulty that he was kept in bed. The salicylates were discontinued after 10 days, without affecting the clinical course. On May 5, 1941 the sedimentation rate had dropped to 40 mm. per hour (Westergren). On May 7, the heart sounds were definitely stronger in quality, chiefly the second mitral sound, but the systolic mitral murmur persisted. The sedimentation rate on May 12 was 27 mm. per hour, and on May 19, 36 mm. per hour. The improvement continued until on May 22 the sounds were of normal quality and the mitral murmur had become much softer. On May 26 the sedimentation rate had dropped to 18 mm. per hour, and on June 2 it finally fell to 5 mm. per hour.

The patient was allowed up on June 2, 1941 and was well for three weeks when headache, fever, and mild abdominal pain recurred. The sedimentation rate at this time was 52 mm. per hour (Westergren) but there were no changes in the heart sounds or cardiac rhythm, and the electrocardiogram showed no changes over the preceding tracings. The patient became asymptomatic and afebrile following this first day, but his sedimentation rate was elevated for three weeks before returning to normal.

All through this illness the paucity of symptoms and lack of findings, other than the cardiac changes, were striking. One could not definitely state that this was rheumatic carditis though it closely simulated it. In an effort to establish a possible cause, immunological studies of the blood for determination of recent hemolytic streptococcus infection were performed. Unfortunately no throat cultures were made at any time.

On May 9, 1941 an antistreptolysin titer was determined at the Arthritis Laboratories of the New York University College of Medicine, and a markedly increased titer (1:1,000) was found. Another determination on May 22, 1941 was 1:2,500, showing a definite rise in the titer and indicating a recent infection with the hemolytic streptococcus. Further antistreptolysin studies were not done.

The subsequent course has been uneventful. The slight mitral murmur disappeared in three months and has never returned. The patient has not developed any additional cardiac murmurs, enlargement, or irregularities of rhythm. After six months of modified rest, he returned to a normal adolescent life without ill effect. He has had several mild respiratory infections but has shown no cardiac changes subsequent to them. At present the patient is serving in the Infantry, having gone through the European Campaign without difficulty, and is entirely well.

## DISCUSSION

It has been known for many years that rheumatic fever and other hemolytic streptococcus infections can affect the conduction system of the heart. As a rule the earliest sign of rheumatic carditis is prolongation of the P-R interval, varying from a transient increase to complete A-V dissociation. It has been believed that these findings were produced by inflammatory changes in the region of the A-V node or the main Bundle of His. However, Bruenn in 1937<sup>4</sup> was the first to show that this interference in A-V conduction might be a vagus effect as the P-R interval could be shortened by atropine. His work has been substantiated by Keith,<sup>5</sup> Wendkos and Noll.<sup>6</sup> More recently, Gubner, Szuchs and Ungerleider<sup>7</sup> reported increasing the P-R interval in acute rheumatic fever by compression of the carotid sinus, a very practical illustration of heightened vagal activity in rheumatic fever. That these changes might not be due to increased vagal tone alone has been suggested by the work of Valy Menken,<sup>8</sup> and Loewi and Navratil.<sup>9</sup> The latter workers have shown that vagal activity is influenced not only by the amount of acetylcholine released by the vagus nerve endings, but also by the rate of destruction of acetylcholine by the tissue enzyme, choline esterase. The activity of the choline esterase is greatly influenced by pH, being most effective in an alkaline pH. Menken<sup>8</sup> has shown that inflammatory tissue tends to lower the pH. It is therefore probable that the lessened activity of choline esterase in inflammatory tissue allows the acetylcholine produced to exert a greater physiological effect on the conduction system than in normal hearts.

As is well known, the vagus exerts its most marked effect on the S-A node, depressing it and producing such states as sinus arrest (S-A block) or A-V nodal rhythm. In view of this physiological mechanism, it can easily be seen how increased vagal tone (or diminished activity of choline esterase) in the case reported could account for the slowing of the impulse rate at the S-A node and produce the ventricular escape noted in figure 1. Apparently there was some impairment of the A-V conduction as well, for in figure 2 there is seen a transient prolongation of the P-R interval which has returned to normal limits in figure 3.

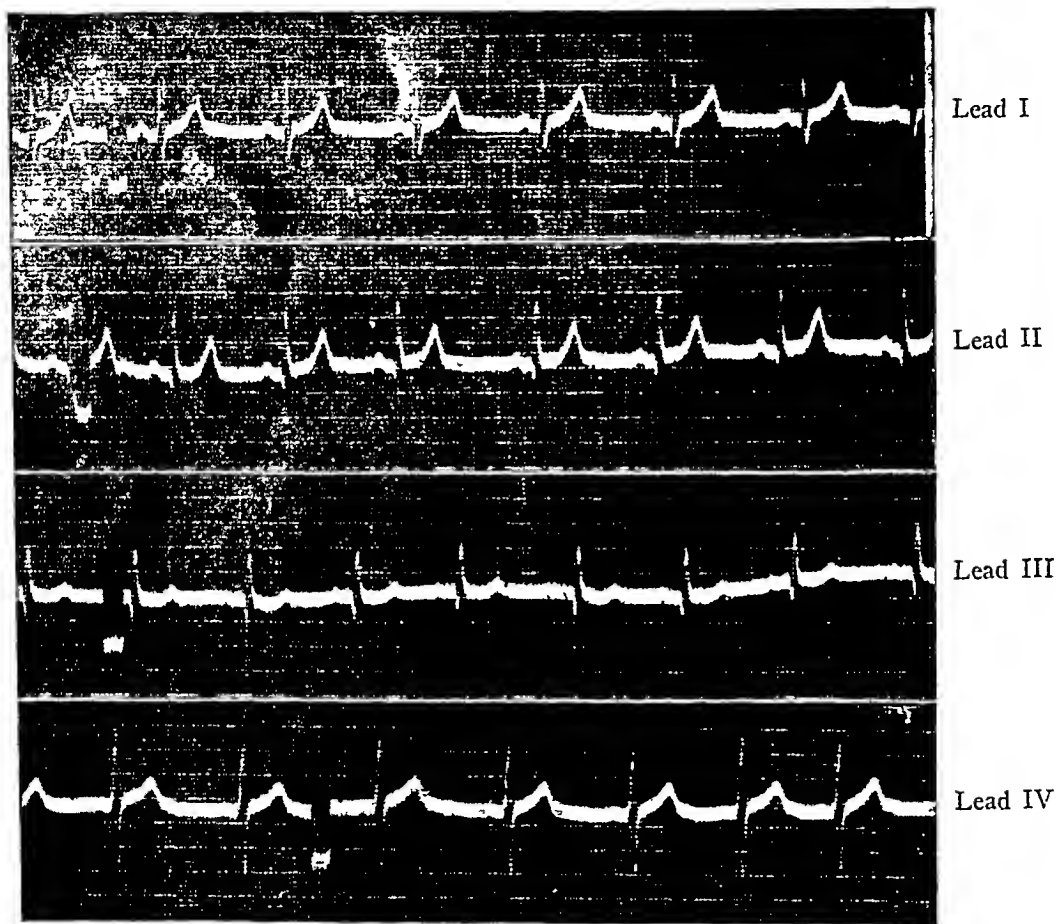


FIG. 3. Electrocardiograms, May 16, 1941.

The site of this increased vagal activity in the case reported—be it rheumatic fever or a closely allied state—is rather unusual in that the primary site of damage seems to have been the S-A node with its subsequent depression, allowing the development of the electrocardiographic pattern reproduced in figure 1. White<sup>10</sup> reported a similar case several years ago in a nurse convalescent from tonsillitis.

In the case reported above an important problem arose as to the etiology of the conduction defect. In the absence of other manifestations of rheumatic fever, it was not believed that a diagnosis of rheumatic carditis could be established. Acute interstitial carditis—so-called Fiedler's disease—was considered,

but ruled out as the patient clinically was too well. No evidence was present of a preceding infectious disease (diphtheria, influenza, typhoid fever, pneumonia, scarlet fever), which might have caused the carditis. It was therefore felt that a study of the antistreptolysin titer might help inasmuch as the hemolytic streptococcus toxin is known to be capable of producing just such an electrocardiographic pattern. The elevated titer on the first examination, with a marked increase two weeks later, definitely indicated that a recent hemolytic streptococcus infection had occurred and was in all likelihood the cause of the carditis. It is felt that this laboratory aid should be utilized when one is dealing with evidence of carditis in which the clinical history and findings do not suggest a definite etiology, since hemolytic streptococcus infection can occur asymptotically.

### CONCLUSIONS

1. A case of carditis of indefinite etiology is presented.
2. By means of study of the antistreptolysin titer it was found that a recent hemolytic streptococcus infection had occurred which most probably was the cause of the carditis.
3. A rather unusual form of conduction defect in carditis—slow sinus arrhythmia with escaped ventricular beats—was found.
4. The pathological physiology accounting for the arrhythmia is briefly discussed.
5. The use of repeated antistreptolysin titer studies is recommended as an important diagnostic aid in cases of carditis of obscure etiology.

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## A CASE OF BACTEREMIA DUE TO AN UNIDENTIFIED GRAM-NEGATIVE PASTEURELLA-LIKE BACILLUS WITH RECOVERY FOLLOWING STREPTOMYCIN THERAPY\*†

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RECENT reports have suggested that streptomycin is of therapeutic value in the treatment of diseases caused by a variety of gram-negative pathogens. Up to the present time, however, the total published clinical data on the use of this antibiotic agent are limited. It seems, therefore, worth while to record a case of bacteremia due to an unidentified gram-negative bacillus in which recovery appeared to follow the use of streptomycin.

### CASE REPORT

*History.* A male, aged 29, was admitted to Bellevue Hospital on December 4, 1945, complaining of chills and fever of three weeks' duration. Five weeks prior to admission the patient was discharged from the army, having served in Louisiana, Mississippi, and the Aleutians. In addition to the chills and fever the patient complained of headache, vomiting and intense pain in the calves, more marked on the right side. There was, however, no swelling of the extremities or skin eruption. For two weeks prior to admission the patient had received a course of combined sulfonamide and penicillin therapy.

The past history was essentially negative.

*Physical Examination.* On admission the patient appeared acutely ill but was well oriented and cooperative. The temperature was 104.8° F., the pulse 92, and the respiratory rate 28. The eyes, ears, nose and throat presented no abnormal findings. The lungs appeared clear. The heart was normal in size and had a regular sinus rhythm. A soft systolic murmur, however, was heard over the entire precordium. There was no enlargement of the liver and the spleen was not felt. Both calves were tender and a suggestive Homans' sign was elicited on the right side. There was no icterus or skin eruption. A few small discrete and moderately tender lymph nodes were felt in the axillae. There was no nuchal rigidity and the reflexes were physiological.

*Laboratory Data.* The red blood cell count was 3,800,000 with 9.5 grams of hemoglobin and the white blood cell count was 7,950 with 88 per cent polymorphonuclears, of which 6 per cent were stab forms. The urine showed a faint trace of albumin and a few white blood cells, but was sterile on culture. The erythrocyte sedimentation rate was 42. A roentgenogram of the chest was reported to show an early pneumonitis on the right side. The electrocardiogram was normal. Several blood smears were negative for malarial plasmodia. Blood agglutinations for typhoid, paratyphoid, typhus, dysentery, brucellosis, meningococcemia, tularemia and infectious mononucleosis were all negative. While the precipitin test for trichinosis was positive in a dilution of 1:1,280, the complement fixation test for this infection was negative on two occasions. The stools failed to show parasites and yielded

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†Streptomycin used in this case was kindly supplied by E. R. Squibb & Sons and by Charles Pfizer & Co.

negative cultures for typhoid, dysentery and salmonella. The spinal fluid was essentially normal. A diagnosis of bacteremia was established, however, when a gram-negative bacillus was isolated from the blood cultures taken on the second and third days following admission.

Despite careful and extensive study the isolated gram-negative bacillus could not be definitely identified. On smear the organism resembled closely *H. influenzae* but it did not require blood for growth. When first isolated it appeared to grow best below the surface in semi-solid media. However, this tendency disappeared quickly and the organism grew luxuriantly on most media at 22° C. and 37° C. The bacillus was non-motile, possessed no capsule and produced acid but not gas from glucose, lactose, sucrose, and levulose. A possible relationship between this bacillus and the Pasteurella group was suggested by Dr. Gregory Schwartzman. When tested for sensitivity to chemotherapeutic agents, the organism was found to be extremely resistant to sulfadiazine and withstood also 20 units of penicillin and 25 units of streptomycin per cubic centimeter.

**Therapy and Course.** For the first six days the patient received only supportive treatment. During this period no subjective or objective changes were noted. The septic temperature continued, showing one or two daily spikes (chart 1). In addition the patient experienced frequent chills, lasting from five to 20 minutes and also bouts of nausea and vomiting. When the positive blood culture was reported on the seventh hospital day, penicillin therapy was begun. Two hundred thousand units of this drug were given on that day, followed by daily doses of 750,000 and later 250,000 units. The total amount of penicillin administered over a period of eight days was 3,950,000 units. In addition the patient received a short course of sulfadiazine for a total of 23 grams. No improvement was noted during the period of combined penicillin and sulfadiazine therapy. Because of the appearance of conjunctival petechiae on the eleventh hospital day and also because of the impression that the apical systolic murmur had become more prolonged and somewhat harsher, the presence of bacterial endocarditis was suspected.

On the fourteenth hospital day, penicillin and sulfadiazine were discontinued and streptomycin administration was started, 125,000 units being given intramuscularly every two hours for 13 days, a total of 16,825,000 units. The day following the institution of streptomycin therapy there was slight but definite amelioration of subjective symptoms but no other significant changes. As shown in chart 1, the blood culture taken on the day streptomycin was started and five subsequent cultures were all sterile. On the twenty-fourth hospital day conjunctival petechiae reappeared. At the same time a suspicious Osler node was noted on the margin of the left palm. The supply of streptomycin was depleted on the twenty-seventh day and none was administered on the twenty-eighth and twenty-ninth hospital days. The patient's temperature nevertheless dropped to normal (chart 1) and, with the exception of a temporary rise to 102° F. on the thirtieth day, was never again elevated above 100° F. From that time clinical improvement was marked and progressive.

Since the presence of bacterial endocarditis was suspected, streptomycin therapy was resumed on the thirtieth hospital day, when the rise in temperature occurred. One-half million units of the drug was given intramuscularly every three hours for 14 days, a total of 52.5 million units. The patient continued to improve steadily and he regained strength and vigor. The apical systolic murmur became less distinct. A slight anemia was still present but the white blood count and the erythrocyte sedimentation rate were both normal. The roentgenogram showed the lungs to be clear and the heart to be of normal size and shape. The patient was discharged on February 9, 1946, the sixty-seventh hospital day, afebrile and completely asymptomatic. During the subsequent three and one-half months he has remained well.

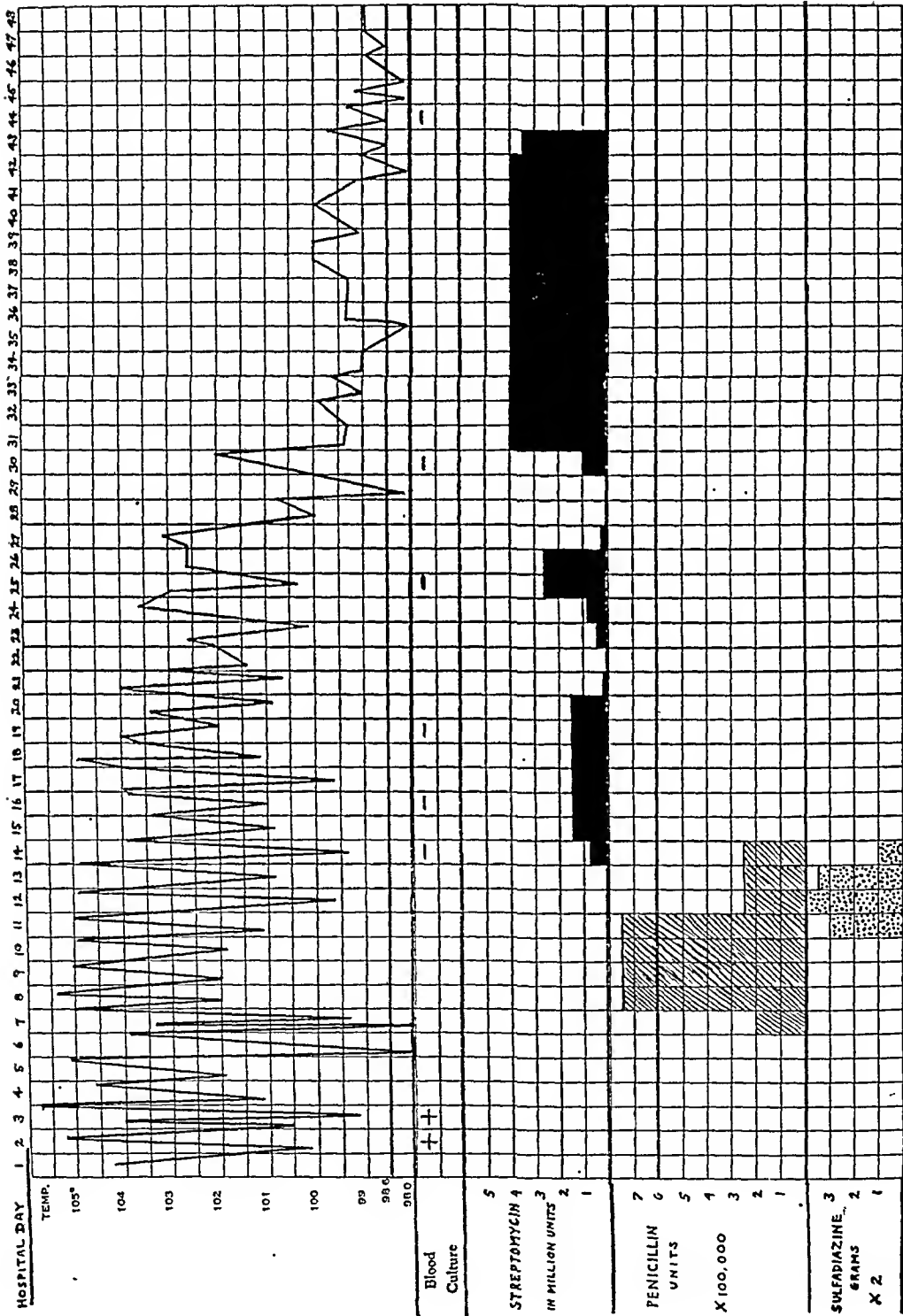


CHART 1. Persistence of septic temperature during course of penicillin and sulfadiazine therapy and fall in temperature following administration of streptomycin.

## COMMENT

The diagnosis of bacteremia was established by two positive blood cultures. The causative organism was a gram-negative bacillus whose identity could not be determined even after exhaustive studies. However, a relationship with the *Pasteurella* group was suggested. Because of the appearance of petechiae, changes in the quality of the apical heart murmur and the presence of a suspicious Osler node, bacterial endocarditis was suspected at one phase of the illness. However, the evidence for this diagnosis seemed insufficient. At the time of the patient's discharge the heart appeared normal except for the presence of a faint systolic apical murmur.

In spite of the organism's resistance and the relatively small amount of streptomycin in the blood (table 1), recovery appeared related to this drug. As

TABLE I  
Streptomycin Blood Levels

Date	Units Per Cubic Centimeter
12-19-45 .....	7.2
12-20-45 .....	4.8
12-28-45 .....	3.0
1-7-46 .....	12.5

Reimann<sup>1</sup> recently pointed out, the susceptibility of an organism to streptomycin and the concentration of the drug in the blood do not bear a strict correlation as regards clinical outcome.

It is, of course, difficult, if not impossible, to rule out spontaneous recovery. Perhaps in support of this is the fact that the blood culture taken on the day streptomycin was instituted, was sterile. On the other hand, the previous use of penicillin and sulfadiazine may have interfered with the result of the blood culture. Unfortunately, para-aminobenzoic acid and penicillinase were not used in the culture media.

## SUMMARY

We have recorded a case of bacteremia due to an unidentified gram-negative *Pasteurella*-like bacillus. The presence of bacterial endocarditis was suspected but could not be established. The patient was treated at first with penicillin and sulfadiazine and then with an intensive course of streptomycin. Recovery in this case seemed to have been brought about by streptomycin.

*Note:* The authors wish to acknowledge their indebtedness to Miss Ruth Gosling and Mrs. Carolyn Falk of the Health Department Bureau of Laboratories and to Dr. Gregory Schwartzman of The Mount Sinai Hospital for valuable assistance and suggestions.

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## CAROTID BODY TUMOR \*

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THE carotid body is an encapsulated, glandular structure located at or near the bifurcation of each common carotid artery. Normally, it is the size of a rice grain or smaller, reaching full development at 20 years. In man, it is difficult to demonstrate the carotid body grossly. Description of the carotid body dates back to 1743, but its functions were not understood until recent years. The carotid bodies (and aortic bodies) are sensory receptors which are stimulated by chemical changes in the arterial blood.<sup>1</sup> This is in contrast to the receptors of the carotid sinus and aortic arch which respond to alterations in arterial pressure, and are, therefore, pressoreceptors. Such chemical factors in the blood as lowered oxygen tension, decreased pH, increased carbon dioxide tension, increased blood temperature, and certain drugs (cyanides, sulfides, nicotine, lobeline, and papaverine) will stimulate the carotid bodies. The physiological response consists of increased respiration, increased sympathetic nervous system activity, and increased cerebral cortical activities. These chemoreceptors are important to man during emergencies such as anoxia, but apparently have no important function under normal conditions, and they are not essential to life.

The gland is thought to be derived from the sympathetic nervous system because chromaffin-positive cells have been demonstrated in its structure. The carotid body, therefore, is thought to be homologous to the medullary portion of the adrenal gland. Histologically the gland is composed of a connective-tissue framework with masses of polyhedral cells grouped about blood capillaries. Large cells may degenerate and form cavities. In addition, many nerves are also present. It has been classed by some writers as a paraganglion, analogous to the adrenals and hypophysis.

Tumors of the carotid body are rare. They have been designated as paragangliomas<sup>2</sup> and peritheliomas.<sup>3</sup> To date, some 200 odd cases have been reported in the literature. Males and females are affected with equal frequency. The majority of cases (70 per cent) occur between the ages of 40 and 60 years. In most instances involvement is unilateral, with no preference for either side of the neck.

It is thought that some disturbance in the course of physiological regression overtakes the gland and results in tumor formation. These tumors exhibit the same histologic character as does the normal gland. Usually they possess an alveolar structure, the alveoli being bordered by delicate capillaries. Occasionally, there is no definite arrangement, and the cells have a diffuse arrangement, so that the appearance suggests a carcinoma. Grossly, the tumors are round, lobulated, encapsulated masses of variable size. On section a vascular, grayish-red or slightly brown appearance is noted. These tumors are usually slow-growing and benign. They have been under observation on the average for six

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to seven years in the reported cases before being excised. In 20 to 30 per cent of cases recurrence has been described, and there are a few reports of lymph node or cerebral metastases.

As a rule, there are no symptoms except for the presence of a slow-growing, painless mass in one side of the neck. When symptoms do occur, they result from invasion of or pressure on adjacent structures, such as the vagus nerve, recurrent laryngeal nerve, sympathetic nerves, pharynx and esophagus. There may be bradycardia, syncope, Stokes-Adams syndrome, dysphonia, hoarseness, dysphagia, headache, tinnitus, exophthalmos or Horner's syndrome.<sup>4</sup>

In only 10 per cent of reported cases of carotid body tumor has the correct diagnosis been made preoperatively. These tumors are commonly confused with branchial cyst, aneurysm, aberrant thyroid gland, tuberculous or non-specific adenopathy, abscess, or metastatic carcinoma. The diagnosis should be considered in all cases of painless, slow-growing tumors situated in the anterior, superior, cervical triangle, which have lateral but not vertical mobility. Occasionally, bulging into the pharynx is noted. Attachment to the skin is never noted. Often, a bruit, thrill, or non-expansile pulsation is present which can be abolished by compressing the carotid artery below the tumor; such compression may temporarily decrease the size of the mass.

Treatment consists of complete surgical removal. Since the carotid vessels are so intimately related to the growth and often pass through it,<sup>5</sup> operation is a formidable procedure. In 50 per cent of cases, it has been found necessary to ligate the carotid vessels, thus accounting for the high operative mortality (25 per cent), death being due to hemiplegia. Post-operative morbidity is similarly high (another 25 per cent) due to injury of adjacent structures at the time of operation. Accurate preoperative diagnosis can reduce the danger of surgery. Prophylactic treatment should be carried out in the form of progressive, systematic compression of the common carotid artery for several weeks. If complete obliteration cannot be withstood without inducing syncope, surgery should not be attempted. Irradiation has been recommended as an alternative in such cases.

#### CASE REPORT

F. M., a 50-year old white male, farmer by occupation, was admitted to the Veteran's Hospital, Aspinwall, Pa., on June 19, 1945 for treatment of "neurocirculatory disturbance and enlarged gland in the neck." The patient had noticed a slowly growing, painless swelling in the left side of his neck for a period of five years. He claimed the mass varied in size from time to time. There had been brief episodes of palpitation during these years. In January, 1945, the patient suffered an illness manifested by extreme weakness, slow pulse (44 per minute), and low blood pressure which confined him to bed under the care of a physician for a period of two weeks. During this illness, he also complained of vague left-sided headaches, mild vertigo, sweating, palpitation and pressure sensations in the left side of his neck. No history of dysphagia, dysphonia or syncope was elicited. The past and family histories were non-contributory.

Examination revealed a well developed and nourished, ambulatory, white male who appeared to be in no acute distress. In the left superior, anterior cervical triangle, under the border of the sternocleidomastoid muscle, there was a round, plum-sized, non-tender mass. The overlying skin was freely movable, but the mass seemed attached to the underlying deep structures; it could be moved readily from

side to side, but had no vertical mobility. The mass was moderately compressible. It did not move when patient swallowed. Pressure on the tumor and adjacent structures of the neck caused no untoward symptoms. The patient's eyes were symmetrically prominent, his pupils were entirely normal, and there was no ptosis. No thermal or moisture changes were noted in the skin of the face and neck. Examination of the heart and lungs was negative. The blood pressure was 120 mm. Hg



FIG. 1. Low power magnification of carotid body tumor.

systolic and 90 mm. diastolic; pulse rate varied between 60 and 64 per minute. There were no other abnormal physical findings.

Laboratory studies revealed a normal blood count and urinalysis. Complement fixation and precipitation tests for syphilis were negative. The electrocardiogram was entirely normal. A teleroentgenogram revealed nothing remarkable in the pulmonary fields or cardiovascular outline.

Diagnoses were made of neurocirculatory asthenia and branchial cyst. On July 7, 1945 operation was performed under sodium pentothal general anesthesia. An extremely vascular, spherical, well-encapsulated tumor, approximately 3 cm. in diameter, was found beneath the upper portion of the left sternocleidomastoid muscle. The tumor pulsated synchronously with the heart and a large artery was seen to enter its lower pole, pass along the antero-medial border, and divide into three branches near the upper pole. Numerous dilated veins covered the entire surface of the tumor.

Digital compression of the large artery entering the tumor produced no untoward symptoms. This vessel and numerous other arteries and veins connected with the tumor were ligated and divided, and the mass excised. The tumor, when sectioned, had a reddish-brown, fairly homogeneous appearance. The operative diagnosis was aberrant thyroid gland.

Microscopic report by the pathologist described a densely cellular tissue without recognizable normal architecture. The stroma contained fibrous strands and large blood vessels. The cells were large, pale, ovoid or vesicular, and were arranged in atypical alveolar nests. In some areas, the cells were closely packed in papillary masses, with densely staining nuclei. The original pathologic impression was papillary adenocarcinoma, origin undetermined.

The post-operative course was entirely uneventful. In view of the pathological report, further clinical studies, a second roentgenogram of the chest, and gastrointestinal roentgenograms were performed in search of a primary malignant focus, but none could be found. Broncho-esophagoscopy was contemplated as the next procedure. At this time, however, a report in the literature was noted describing a tumor of the carotid body,<sup>6</sup> which immediately brought to mind our case. A review of the clinical picture and microscopic section (figure 1) confirmed this diagnosis. The patient was discharged from the hospital in good health on August 1, 1945.

#### SUMMARY

A case report and brief review of carotid body tumors have been presented. Surgical removal of the tumor in our case was performed uneventfully, despite failure to make the correct preoperative diagnosis. This condition should be considered in all tumors of the anterior cervical triangle so that correct treatment may be instituted prior to operation.

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#### VISCERAL LEISHMANIASIS (KALA-AZAR): REPORT OF A CASE \*

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VISCERAL leishmaniasis (kala-azar) is a chronic and, in untreated cases, a highly fatal infectious disease characterized by a persistent fever of an alternating, remittent, or intermittent type, progressive weight loss, weakness and emaciation,

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progressive anemia, splenomegaly and hepatomegaly, severe reduction of the leukocytes, particularly of the granulocytes, and by the demonstrable presence of the causative parasite in the spleen and bone marrow. The disease is produced by the protozoan, *Leishmania donovani* which is transmitted from person to person by the bite of one or more species of blood sucking sandflies of the genus *phlebotomus*.<sup>1</sup> There is a possibility that the disease may be transmitted also through the ingestion of contaminated food or drink or by droplet infection.<sup>2</sup> In the human host the protozoan appears in the form of inclusion bodies (Leishman-Donovan bodies), but in the intermediate host and upon culture (NNN medium) the *Leishmania* assumes a leptomonad (flagellated) form. The disease is ordinarily considered a tropical disease, though it actually occurs endemically and epidemically in southern Russia, India, China, the Near East, the Mediterranean basin, and in other parts of Africa and Asia. More recently cases of visceral leishmaniasis have been reported from South America.

The onset of visceral leishmaniasis is ordinarily insidious and its course is characterized frequently by remissions and exacerbations. Occasionally the onset is acute and the course, rapidly fatal. The fever may be intermittent, remittent, or sustained and is characterized by diurnal remissions at some stage of the disease in 25 to 50 per cent of cases. There is progressive weight loss and weakness leading to profound emaciation. Enlargement of the spleen is progressive and not infrequently the lower border can be palpated below the level of the umbilicus. The large size and firm consistency of the spleen contrasts with the softer, smaller spleen observed in typhoid fever and in malaria. Ordinarily the enlargement of the liver occurs later and is less conspicuous than that of the spleen. There is a progressive anemia, ordinarily of a normochromic, normocytic or macrocytic type. The total white blood count is markedly depressed, frequently to 1,000 or 2,000 cells, and the granulocytes constitute only 5 to 20 per cent of the total count. The fatality rate in untreated cases approaches 90 per cent. Death is ordinarily the result of intercurrent infection.

The diagnosis is established by clinical and laboratory observations. There is a history of residence in an area in which the disease is endemic and of the possible exposure of the patient to the bite of a sandfly. There are the physical findings of weakness, emaciation, hepatomegaly, splenomegaly, and, frequently, the typical fever. The anemia and the leukopenia are demonstrated by a blood count. Inclusion bodies typical of the disease may be recovered in material obtained by splenic, or sternal puncture and rarely from the peripheral blood. The leptomonad form of the parasite may be demonstrated by culture of the blood, preferably that from the spleen, or marrow, on NNN medium. Corroborative laboratory tests include the aldehyde (formol-gel) test of Napier, the neostibosan test, the water-precipitation test (globulin-precipitation test, Ray's test) and the complement-fixation test.<sup>3</sup> The differential diagnosis includes malaria, typhoid fever, other diseases producing enlargement of the spleen, and hemopoietic diseases producing anemia and leukopenia.

Complications include a specific dysentery due to severe infection of the intestine with *Leishmania*, hemorrhagic phenomena, cutaneous lesions due to the disease itself, secondary bacterial invasion due to the generally lowered resistance and to the defective phagocytic power of the blood, and, as is frequently the case with tropical diseases, the presence of other endemic tropical infections.

Specific treatment with antimony compounds is highly successful.<sup>4</sup> Pioneer treatment with trivalent antimony compounds (potassium antimony tartrate and Fuadin) was only moderately successful and was associated with relatively frequent toxic reactions. Pentavalent antimony compounds, of which the most commonly used are Neostam (Burroughs and Wellcome) and Neostibosan (Winthrop), give a high percentage of cures and fewer toxic reactions. These compounds in doses of 0.2 to 0.3 gram are injected intravenously on alternate days until a total dose of 3.0 to 6.0 grams has been administered. In resistant cases a subsequent course of treatment may be necessary, but should not be given immediately since clinical improvement and the disappearance of the parasite from the blood may not occur for several weeks after the completion of any single course of treatment. Supportive treatment should include a diet high in calories, protein and vitamins, supplemented by parenteral therapy as necessary. Blood transfusions are indicated frequently.

The following case illustrates the classical history, symptoms, signs and course of the disease as modified by adequate pentavalent antimony treatment, which, in this instance, included two courses. An additional feature is the concurrent tertian malaria which was treated promptly and effectively.

#### CASE REPORT

A 24 year old white male entered an AAF Regional and Convalescent Hospital, on December 16, 1944 complaining of chills and fever every third or fourth day for about three weeks.

The patient's past history, prior to his overseas service, was not remarkable. Parents and siblings were alive and well and there was no history of familial disease. He had gone overseas in November 1941 and had spent 34 months in India. He had never taken suppressive treatment for malaria during his overseas service. He had experienced several attacks of chills and fever during the time spent in India and was treated with quinine on one occasion in 1943. Other attacks of chills and fever, which he assumed to be malaria, were self-treated with quinine. There had been several attacks of diarrhea in India, but he had never been hospitalized and no attempt had been made to determine the cause of these attacks. He was hospitalized in India for three weeks because of jaundice, the etiology of which remained unknown. The patient returned to the United States on November 18, 1944 and six days later suffered an attack of chills and fever which recurred every third or fourth day until hospital admission. There had been some abdominal pain for a fortnight prior to entry, but no vomiting or diarrhea. There had been a mildly productive cough, profuse night-sweats and some nausea in the mornings, with an associated weight loss of 15 pounds in the two months prior to entry. The patient complained of irritability, nervousness and insomnia.

Upon admission, the patient appeared acutely ill and exhibited great weight loss and emaciation. His skin was warm and dry. Ears, eyes, nose and throat were normal and there were no findings of significance in the chest. The liver edge was felt two centimeters below the costal margin and was slightly tender, while the edge of the spleen was palpable below the level of the umbilicus, but was not tender. There were small palpable lymph glands in the cervical, axillary, epitrochlear and inguinal regions. The skin was pale and did not exhibit the dusky color frequently described in patients with kala-azar. Laboratory observations, on admission and subsequently, are summarized in charts 1 and 2.

A course of atabrine therapy, starting with an intramuscular injection of 0.4 gram and continuing with 0.1 gram three times a day orally, was given despite the

failure to demonstrate plasmodia in the peripheral blood. There was transient improvement on this therapy, but it soon became apparent that the response was incomplete. Malarial parasites were never demonstrated in the blood in the hospital laboratory, but were discovered in smears of splenic blood sent to the Army Medical Center. The possibility of visceral leishmaniasis was considered because of these facts: (1) The patient had spent 34 months in an endemic region in India; (2) The diurnal remissions in the fever (figure 1); (3) The enlarged liver and spleen; and

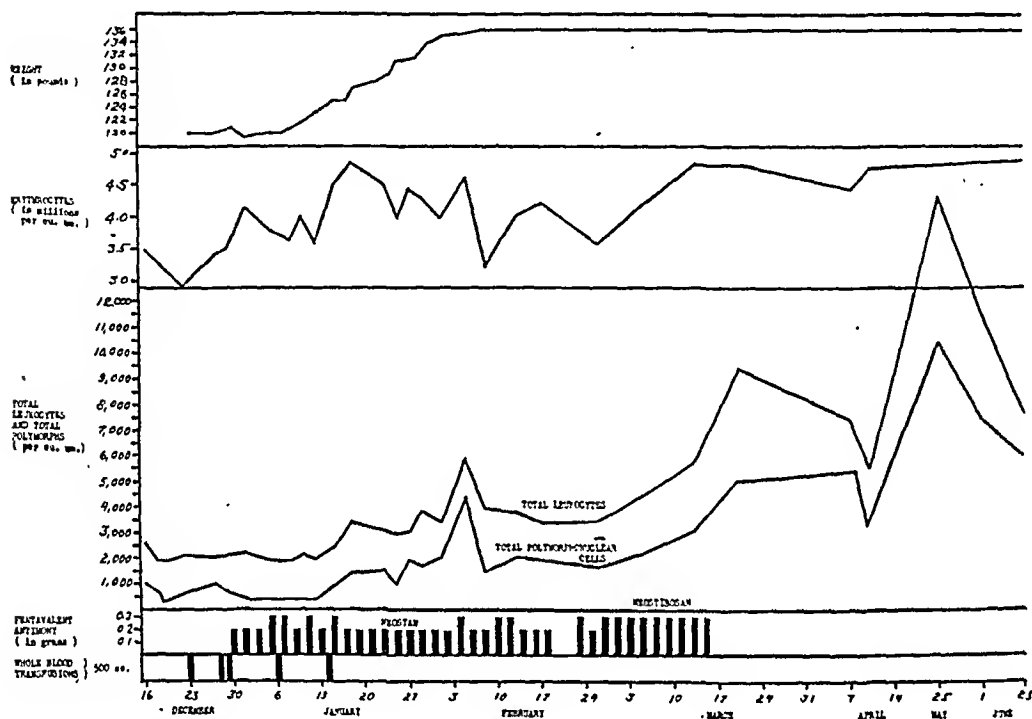


CHART 1.

(4) The blood findings which included an anemia and a leukopenia with relative lymphocytosis. The diagnosis was confused by the report of a positive agglutination in high titer for typhoid H-antigen. Confusion persisted when a slow lactose-fermenting gram-negative bacillus was obtained from the stool. A sternal marrow puncture on the tenth day of hospitalization failed to reveal Leishman-Donovan bodies. Five indirect transfusions of 500 cubic centimeters of whole blood were given between December 23, 1944 and January 17, 1945 to combat the anemia and emaciation and the patient's condition, despite the daily high fever, improved somewhat. On December 29, 1944 a sternal and a splenic puncture were done and large numbers of inclusion bodies typical of those found in visceral leishmaniasis were demonstrated in smears of material obtained from both of these sources.

Specific treatment for leishmaniasis was initiated on December 30, 1944 when 0.2 gram of Neostam was given intravenously without untoward reaction. Treatment was continued according to the schedule in chart 1, with Neostam given intravenously in doses of 0.2 or 0.3 gram on alternate days through February 18, 1945, a total number of 26 injections and a total dose of 6.2 grams of Neostam. On February 25, 0.2 gram of Neostibosan was given intravenously and this was followed with injections of 0.3 gram on alternate days until 10 injections had been given, a total dose of 2.9 grams of Neostibosan. Other medications given during the entire

course of hospitalization included oral and parenteral vitamins B and C, ferrous sulfate, sedation as necessary and a high caloric diet.

Splenic punctures were performed on December 23 and 29, 1944 and on January 29, 1945. Leishman-Donovan bodies were demonstrated by smear and the leptomonad form of the parasite by culture on each occasion.

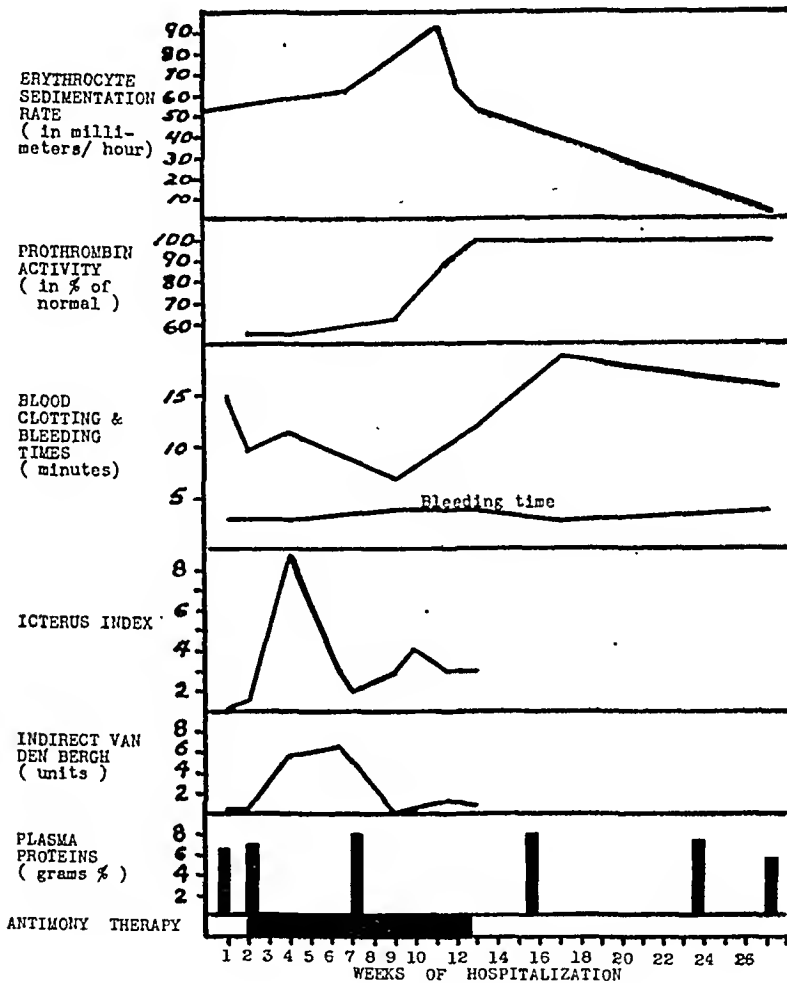


CHART 2.

The first indication of improvement occurred during the first week in January when the temperature curve started downward and the diurnal remissions ceased (figure 1). There was a slow, but general subjective and objective improvement which began at about this same time and the patient's weight increased slowly from 120 to 136 pounds (chart 1). There was a transient clinical jaundice following an injection of Neostam on January 11, but this disappeared overnight. The edge of the spleen could be palpated below the umbilicus until the middle of February at which time it was noted that the organ, previously oval in contour, had become more pancake shaped. The spleen was definitely smaller and had receded upward two or more centimeters by the middle of March.

Laboratory studies, presented graphically in charts 1 and 2, are summarized as follows: The moderately severe anemia present on admission was improved transiently during the latter part of January, but was not permanently corrected until the

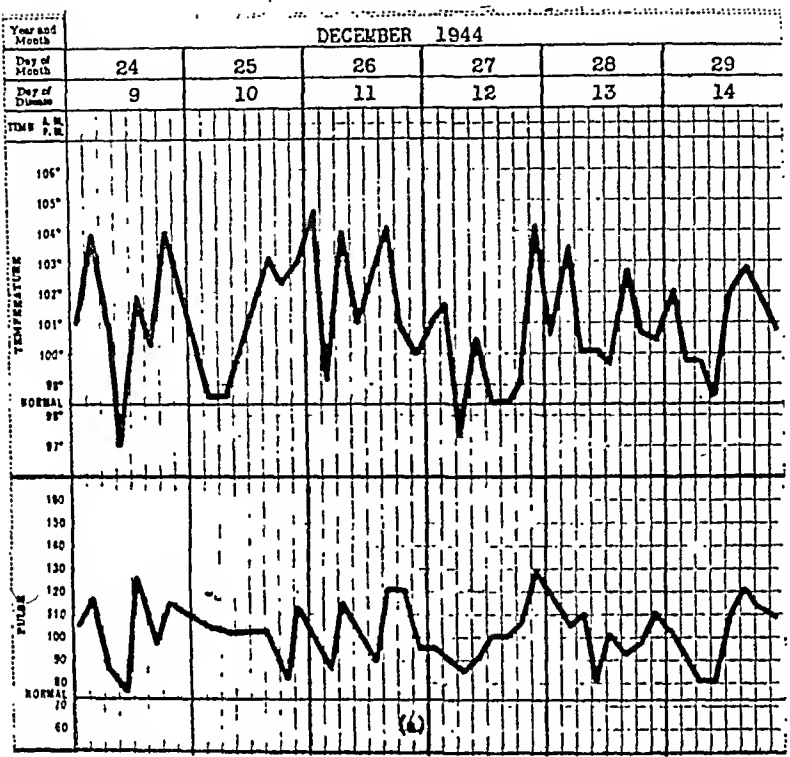


FIG. 1. Graphic records of the temperature and the pulse curves typical of various periods during hospitalization. (a) Observations from the ninth through the fourteenth day, before specific pentavalent antimony therapy had been initiated. Note the diurnal remissions in the temperature curve. The pulse rate is elevated roughly in proportion to the temperature.

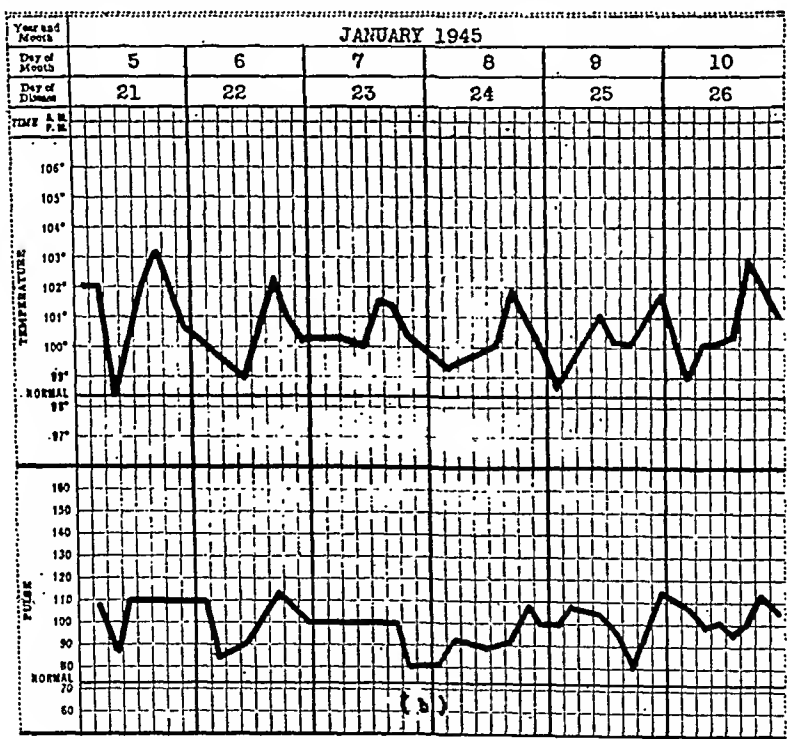


FIG. 1. (b). Observations from the twenty-first through the twenty-sixth day, early in the course of treatment with Neostam. Temperature curve is lower and does not exhibit diurnal remissions.

middle of March. The total white blood count was reduced to 2,600 cells on entry and the lowest count was 1,800 cells. The total count remained at a level of approximately 2,000 cells per cubic millimeter until the middle of January when it began to increase in a slow curve. The polymorphonuclear cells were proportionately reduced, reaching a minimum of 17 per cent on January 10, but increasing in proportion to the total white blood count after the middle of January. The urine did not at any

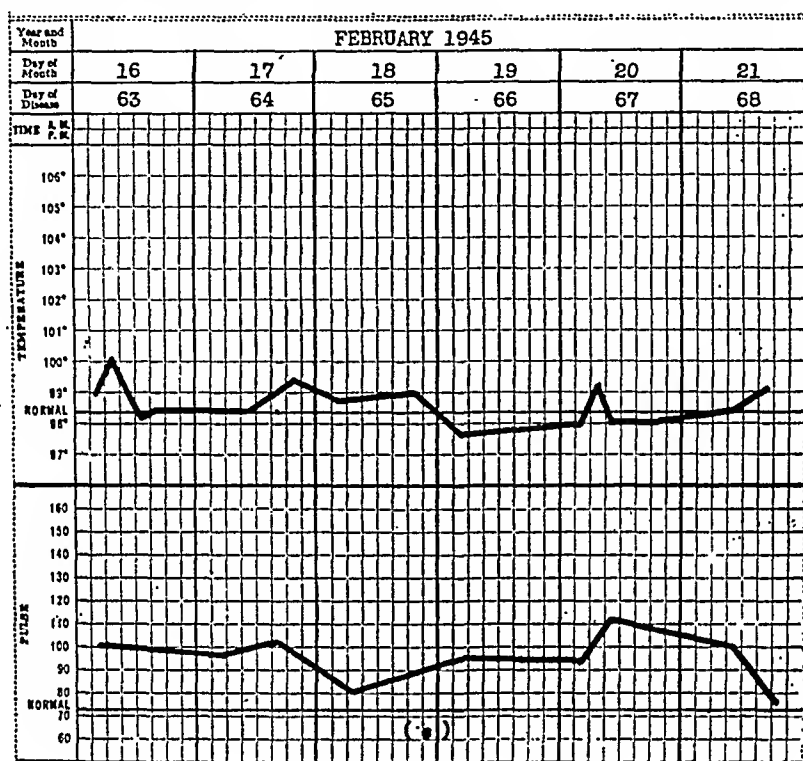


FIG. 1 (c). Observations from the sixty-third through the sixty-eighth day, late in the course of Neostam therapy. Note the relatively flat temperature curve, but the persistent elevation of the pulse rate.

time contain more than a trace of albumin and a few pus cells. The sedimentation rate was extremely rapid through March, but was normal in June 1945. The plasma proteins were consistently normal in amount and the albumin-globulin ratio was not disturbed. The bleeding time was not prolonged at any time, but the clotting time, as determined by the Lee-White method, was ordinarily above the limits of normal. Prothrombin activity was reduced to about 50 per cent of normal activity during the first month, but slowly increased to 100 per cent of normal activity during antimony therapy and remained at a normal level. At no time was the icterus index above normal, but the indirect Van den Bergh reaction was slightly elevated during treatment. The aldehyde test of Napier was repeatedly negative except on one occasion during early March, at which time a positive water-precipitation reaction also was obtained. The neostibosan test was negative. A variety of miscellaneous laboratory procedures, performed from time to time, were normal.

The patient was transferred to Moore General Hospital on March 29, 1945. He complained of weakness and his weight was five pounds below his usual level. Physical examination was unremarkable except for the enlarged spleen which could be felt two centimeters below the costal margin. Except for a mild intercurrent infection, the patient was asymptomatic during his stay at the general hospital. A splenic

puncture was performed on April 27, 1945 and stained smears, cultures and inoculation of a Hamster with material so obtained failed to demonstrate *Leishmania donovani* in any form. Laboratory studies, included in charts 1 and 2, were normal except for a positive complement-fixation test for kala-azar, a positive cephalin-cholesterol flocculation test, and a prolonged blood clotting time. The patient was returned to the Regional and Convalescent Hospital, on June 21, 1945, without further treatment and considered as cured.

Examination upon reentry to the Regional Hospital revealed a well nourished male who exhibited none of the stigmata of chronic disease. The only abnormality upon physical examination was a palpable spleen, felt two to three centimeters below the left costal margin. Laboratory studies (charts 1 and 2) were normal except for the prolonged clotting time of the blood. The course on the ward was afebrile and uneventful and the patient was discharged as cured.

### DISCUSSION

This patient demonstrated the classical clinical signs and laboratory findings of severe visceral leishmaniasis upon his initial admission to this hospital. Of particular interest is the temperature curve which presented diurnal remissions until modified by the effects of antimony therapy. The response to treatment with pentavalent antimony compounds, though delayed, was eventually satisfactory. The need for relatively large amounts of antimony and protracted treatment therewith may have been due to a long-standing infection by *Leishmania donovani*. One or more of the several illnesses which the patient experienced in India, the repeated attacks of chills and fever, the recurrent diarrheas, or the jaundice, may have represented earlier acute episodes of visceral leishmaniasis. The impression was gained that improvement was more rapid under treatment by Neostibosan than during the course of Neostam. This was supported by the patient's statements as to his subjective improvement. Accelerated improvement during treatment with Neostibosan might be explained by the accumulated effect of the total amount of antimony administered rather than to the relative efficacy of the two compounds. However, during the latter period of treatment with Neostam there was some relapse in the patient's feeling of well-being, and a definite relapse of his anemia and leukopenia (chart 1). That these untoward effects may have been the result of toxic effects of Neostam is suggested by the clinical jaundice following one injection, by the occasional nausea and vomiting which followed other injections and by the elevation of the indirect Van den Bergh reaction during treatment with Neostam (chart 2).

The causative organism was demonstrated repeatedly in material obtained from the spleen and the bone marrow and positive reactions were obtained on at least one occasion with three of the four confirmatory tests for the disease. The hematological changes, anemia, leukopenia and granulocytopenia, and their correction under specific therapy were classical. That the blood cytology remained at normal levels as long as the patient was observed, a period of three and one-half months following completion of antimony therapy, was evidence for the success of treatment. The delayed blood coagulation time, a well-recognized feature of the disease,<sup>2</sup> was improved only transiently under treatment, although the bleeding time was normal on all occasions. The prothrombin activity was greatly reduced initially, but improved steadily under treatment until a normal level was reached and maintained. Reduction of prothrombin activity

in visceral leishmaniasis has been observed previously.<sup>5</sup> The erythrocyte sedimentation rate was greatly accelerated upon admission and throughout treatment, but was normal four months later. It is stated that the erythrocyte sedimentation rate is probably greater in kala-azar than in any other disease,<sup>2</sup> but such a statement must be questioned until it is determined that observed rates have been corrected for the effect of the ordinarily concurrent anemia. Altered sedimentation rate of the erythrocytes might well be anticipated in the majority of cases since it has been shown that there is an increase in the globulin fraction of the plasma, particularly in the euglobulin fraction in the disease. However, in the case presented, several determinations of the albumin-globulin fractions of blood proteins failed to demonstrate any increase in globulin. Blood platelet counts were not done, but there was no evidence of hemorrhagic phenomena at any time.

At the time of the patient's release from the hospital, four months after the completion of antimony therapy, he had accomplished completely, or to a satisfactory degree, all criteria for cure of the disease, namely, recovery of weight and strength, establishment of normal blood cytology and biochemistry (except for the prolonged clotting time), complete recession of the liver and satisfactory, although incomplete recession of the spleen, and the absence of the parasite upon smear, culture and Hamster inoculation of material obtained by splenic puncture.

### SUMMARY

A case presenting the classical clinical features and laboratory observations of visceral leishmaniasis with apparent cure following treatment with pentavalent antimony compounds is presented in detail. The ordinarily accepted criteria of cure were satisfactorily observed and maintained for four months following the completion of treatment.

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## EDITORIAL

### *GENETIC ASPECTS OF SOME DISEASES OF THE BLOOD*

PRECISION in diagnosis, prognosis and therapy depends to a large degree on exactness in etiology. One cause, and by no means an unimportant one, of clinical abnormality is the gene. Major emphasis in the control of disease has been placed upon environmental factors in their broadest sense. Thus tremendous strides have been made in recent years in the control of diseases of infectious or nutritional etiology. As the latter continue to be conquered one by one the influence of genetic anomalies becomes of greater relative importance.

The use of the term "congenital" in delineating disease of genetic origin is, as Crew<sup>1</sup> points out, both mistaken and misleading. Congenital refers to a point in time rather than a cause. Even in this regard its use is inexact since a characteristic present at birth was in the majority of instances present in the fetus during intrauterine existence. The recent evidence that a virus infection, Rubella, occurring in the mother during the early months of pregnancy affects the development of the fetus, is an outstanding example of an extra-chromosomal factor resulting in "congenital" disease. Gregg,<sup>2</sup> in Australia, in 1941, first noted the high incidence of infants with congenital cataracts born to such women. It is interesting to note that a significant number of these children were likewise afflicted with deaf-mutism and congenital heart defects.

Even though the disease entity be of genic origin, the implication of heredity as a factor in etiology is not an indication that further medical progress is impossible. On the contrary, clear understanding of the genetic mechanisms offers hope of eventual control.

Among recent contributions of the relatively young science of human genetics to clinical medicine may be mentioned the elucidation of the hereditary aspects of two varieties of so-called "erythroblastic anemia." Reference is made on the one hand to the constellation of entities known as Cooley's or Mediterranean anemia and on the other to the group collectively called Erythroblastosis Fetalis. In 1925, Cooley and Lee<sup>3</sup> first demarcated a blood dyscrasia, apparently limited to children, from the miscellaneous group known as von Jaksch's anemia or "anemia infantum pseudoleucemica." Although designated for some years as a purely pediatric syndrome it has within recent time invaded the field of adult medicine as a result of the detection of a "carrier state" or mild variety of the disease. In its classical

<sup>1</sup> CREW, F. A. E.: The place of genetics in clinical medicine, *British Med. Bull.*, 1946, iv, 166-170.

<sup>2</sup> GREGG, N. McA.: Congenital cataract following German measles in mother, *Trans. Ophth. Soc. Aust.*, 1941, iii, 35.

<sup>3</sup> COOLEY, T. B., and LEE, P.: Series of cases of splenomegaly in children with anemia and peculiar bone change, *Trans. Am. Pediat. Soc.*, 1925, xxxvii, 29.

form the disease is characterized as a chronic, progressive hypochromic microcytic anemia. The peripheral blood contains numerous normoblasts and there is a remarkable degree of anisocytosis and poikilocytosis, the latter frequently being ovalocytes and so-called "target cells." When exposed to the action of hypotonic salt solutions, the cells show decreased fragility, a characteristic apparently dependent upon their abnormal thinness (leptocytosis). Splenomegaly, deposition of large quantities of iron-containing pigment in the viscera, characteristic mongoloid facies and skeletal changes are among the outstanding clinical and pathological features. The racial limitation to inhabitants, or descendants of inhabitants, of the Mediterranean littoral was early noted. Subsequent studies have revealed a handful of typical cases in other racial stocks. Cooley's comments<sup>4</sup> upon the latter phenomenon are particularly apt, "When a disease-producing (genic) mutation takes place, it recurs first in the neighborhood of its origin. It is limited to a race in proportion to the clannishness and isolation of the people involved. The appearance in a negro or Chinese child must not be attributed to an unlikely racial cross. Such occurrences may be explained on the new appearance of mutations which set up new foci of the disease."

Since the severe variety of Mediterranean anemia was apparently incompatible with life beyond childhood, hereditary transmission was at first deemed unlikely. The existence of a genetic etiological factor was, however, suggested by the studies of Angelini<sup>5</sup> and Caminopetros<sup>6</sup> of parents of typical cases. In 1940 and 1941<sup>7,8,9</sup> several groups of investigators independently described a syndrome in adults of Italian descent characterized by splenomegaly, at times a slight microcytic anemia, slight hyperbilirubinemia, skeletal changes demonstrable by roentgen-ray and *decreased fragility of the erythrocytes*. The presence of "target" cells was considered by some as pathognomonic of the state, but subsequent studies have indicated the non-specificity of this finding. The final link was completed between this relatively mild, frequently asymptomatic, state and typical Thalassemia (derived from the Greek word for Mediterranean) by demonstration of characteristic changes in the blood of *both parents* of children with Cooley's anemia. Decreased fragility of the red cells is a striking feature of both syndromes.

The patient with Cooley's anemia is considered now to have inherited from each of his parents the gene responsible for the entity, i.e., he is

<sup>4</sup> COOLEY, T. B.: Hereditary factors in the blood dyscrasias, *Am. Jr. Dis. Child.*, 1941, lxii, 1-8.

<sup>5</sup> ANGELINI, V.: Primi risultati di ricerche ematologiche nei familiari di Ammalati di anemia di Cooley, *Minerva med.*, 1937, ii, 331.

<sup>6</sup> CAMINOPESTROS, J.: Researches on infantile erythroblastic anemia in people of eastern Mediterranean, *Ann. de Med.*, 1938, xliii, 27-61, 104-125.

<sup>7</sup> WINTROBE, M. M., MATTHEWS, E., POLLACK, R., and DOHYNS, B. M.: A familial hemopoietic disorder in Italian adolescents and adults, *Jr. Am. Med. Assoc.*, 1940, cxiv, 1530.

<sup>8</sup> DAMESHEK, W.: Target cell anemia. Anerythroblastic type of Cooley's erythroblastic anemia, *Am. Jr. Med. Sci.*, 1940, cc, 445.

<sup>9</sup> STRAUSS, M. B., DALAND, G. A., and FOX, H. J.: Familial microcytic anemia, *Am. Jr. Med. Sci.*, 1941, cci, 30.

homozygous in regard to this gene. Neel and Valentine<sup>10</sup> designate this variety of the disease as *Thalassemia Major*. The heterozygote, i.e., the individual with but one abnormal gene inherited from one parent will demonstrate the milder variety of the disease, referred to as *Thalassemia Minor* by Valentine and Neel. The latter investigators believe it to be inherited either as an incomplete recessive or semi-dominant character. Prior to 1942 *Thalassemia* had been regarded as a relatively rare entity, less than one hundred cases having been recorded up to that time. Survey of the hospital records in Rochester, N. Y. by Neel and Valentine<sup>11</sup> in 1945 resulted in the discovery of 11 cases occurring between 1928 and 1942. During a similar period it was estimated that 26,044 children of Italian parentage were born in this community. Thus the disease occurred once in 2368 births. From these data and employing the genetic concept mentioned above, it was estimated that *Thalassemia Minor* occurs in approximately one in 25 Italians. This estimate has not yet been validated by direct studies of representative samplings.

*Thalassemia* is the first inherited disease of medical importance in which it is possible by appropriate laboratory means to detect carriers. Recently electroencephalographic studies have permitted similar observations in epilepsy.<sup>12</sup> The clinical significance of *Thalassemia Minor* has yet to be evaluated carefully. Many persons compensate for their individually deficient erythrocytes by an increased red cell count. Others fail to make this adjustment and go through life with subnormal values for hemoglobin and red blood cells. It seems probable that they are handicapped to the same extent as individuals with an iron-deficiency anemia of comparable degree with the added disadvantage that this is a chronic disorder. Clinical characteristics indicate that *Thalassemia Minor* must be considered in the differential diagnosis of such entities as rheumatic fever, plumbism, atypical hemolytic jaundice and splenomegalies of undetermined etiology.

The genetic characteristics of the various antigens which determine blood groups have been intensively studied and the literature is voluminous. Serologic study of numerous pedigrees enabled Bernstein<sup>13</sup> to evolve a theory regarding the inheritance of blood groups which has apparently withstood the test of time. Blood group inheritance depends upon the presence, at a particular locus of a pair of chromosomes, of one of a group of three genes. Since the three genes responsible for the antigens A, B and O of the erythrocyte can only occupy individually a single locus they are termed multiple allelomorphs or alleles. In this series A and B are of equal dominance while O is recessive to each of them. Similar investigations have

<sup>10</sup> VALENTINE, W. N., and NEEL, J. V.: Hematologic and genetic study of the transmission of *Thalassemia* (Cooley's anemia, Mediterranean anemia), *Arch. Int. Med.*, 1944, lxxiv, 185.

<sup>11</sup> NEEL, J. V., and VALENTINE, W. N.: The frequency of *thalassemia*, *Am. Jr. Med. Sci.*, 1945, ccix, 568.

<sup>12</sup> PENFIELD, W., and ERICKSON, T. C.: *Epilepsy and cerebral localization*, 1941, C. C. Thomas, Springfield, Ill.

<sup>13</sup> BERNSTEIN: *Ztschr. f. indukt. Abstammungs v. Vererbungs.*, 1925, xxxvii, 237.

been made of the agglutinogens M, N and P as well as of the phenomenon concerned with the presence or absence of the A, B, O antigens in various tissues and secretions of the body (the secretor, non-secretor mechanism). The characteristics determined by these genes are entirely normal and have apparently little to do with clinical syndromes. Yet their significance for forensic medicine and anthropology cannot be gainsaid. Recent studies, however, point out some fundamental eugenic aspects of this knowledge. Waterhouse and Hogben<sup>14</sup> have recently published a statistical study of the blood groups of offspring of mothers belonging to group O. In children resulting from the mating of a group O mother with a group A father there was a net deficiency of 25 per cent Group A children. They calculated that 8 per cent of all group A children concerned died; this represented 3 per cent of all conceptions. A pregnancy in which the mother is of one blood group while the fetus is of another is termed a "heterospecific" pregnancy. Further facts were also adduced, but are chiefly of evolutionary interest.

More clinical interest attaches to the study of heterospecific pregnancies with regard to the recently discovered Rh antigen of human erythrocytes. Ample proof now exists for the predominant importance of Rh incompatibility in the etiology of erythroblastosis fetalis.<sup>15</sup> The significance of Rh incompatibility in the causation of hemolytic transfusion reactions has also been amply demonstrated. It may be of interest to review briefly some of the newer genetic concepts regarding the Rh factor.

When first discovered, the Rh antigen was believed to be inherited on the basis of a single gene Rh and its recessive allele, rh. Human genotypes then were considered to be of three varieties, Rh Rh, Rh rh, and rh rh. Subsequent discovery of antibodies of different specificity indicated that the Rh antigen was not a single homogenous entity but rather that there were a variety of closely related Rh antigens within the erythrocyte. Weiner<sup>16</sup> postulated that there were actually six allelic genes which might individually occupy a single locus in a chromosome. In 1941, Levine<sup>17</sup> described, on the basis of an antibody discovered in the serum of the mother of an erythroblastotic infant, another antigen of the human red cell which, because of its close but reciprocal relationship to Rh, he called Hr. The necessity of including this antigen within the sphere of the Rh group of antigens led to the proposal of another theory of the inheritance of Rh blood types by Fisher and Race.<sup>18</sup> The latter theory seems thus far to conform more readily to actual clinical and laboratory findings. The Fisher-Race theory proposes that there are three closely linked pairs of genes which determine the Rh and Hr phenotypes (definitive type) of an individual. These genes are

<sup>14</sup> WATERHOUSE, J. A. H., and HOGBEN, L.: Incompatibility of mother and fetus with respect to the iso-agglutinin A and its antibody, *British Jr. Soc. Med.*, 1947, i, 1.

<sup>15</sup> LEVINE, P.: The present status of the Rh factor, *Am. Jr. Clin. Path.*, 1946, xvi, 597.

<sup>16</sup> WEINER, A. S.: The Rh series of allelic genes, *Science*, 1944, c, 595.

<sup>17</sup> LEVINE, P.: Yearbook of pathology and bacteriology, 1941, pp. 508-513.

<sup>18</sup> FISHER, R. A., and RACE, R. R.: Rh gene frequencies in Britain, *Nature*, 1946, clvii, 48.

designated C-c, D-d, E-e. Appropriate combinations of these result in the definite type of the individual.

This may be looked upon as an example of the results which may be obtained by the fruitful collaboration of the geneticist and the clinician. Erythroblastosis fetalis occurs approximately once in every 200 births, an incidence of about 0.5 per cent.<sup>19</sup> It has heretofore had a high mortality. By appropriate laboratory study it is now possible to predict its occurrence with a high degree of accuracy. Successful therapy of this disease of genetic etiology is perhaps not too far distant.

M. S. S.

<sup>19</sup> SACKS, M. S., KUHNS, W., and JAHN, E. E.: Studies in Rh iso-immunization, Am. Jr. Obst. and Gynec. (in press).

## REVIEWS

*The Nervous Child.* By H. C. CAMERON, M.D. 252 pages; 19 × 12.5 cm. 1946. Oxford University Press, New York.

In his fifth edition, Dr. Cameron has preserved the keen insight into the emotional and social factors in children's illness and behavior, that has made the book a valuable contribution through the last 20 years. One would wish that the author in this revision might have given more attention to the modernization of the medical details that accompany his observations and interpretation of children's problems. Under his discussion of the treatment of rheumatism and chorea (p. 19) he states "it is purely symptomatic," disregarding the contribution of fever therapy and other recent advances in this field. The present day pediatrician will shun his "mechanical restraint" (p. 99) therapy of masturbation, even as a last resort. Despite the book's inadequacy in reviewing some of the present day therapeutic resources, it still is an excellent attitude building tool to introduce medical students and practitioners to the art of managing skillfully the psychosomatic factors operating in medical practice with children.

W. G. H.

*Narco-analysis.* By J. STEPHEN HORSLEY, M.D. 134 pages; 19 × 13 cm. 1946. Oxford University Press, New York. Price, \$2.50.

This short and very readable book is a useful addition to the library of any hospital where psychiatric patients are treated. It discusses the chemistry and physiology of various barbiturates and the theories underlying narcotic hypnosis and therapy. As was demonstrated, particularly during the recent war, the results of this method of treatment are most striking in relieving patients with traumatic neurosis of recent origin. The material revealed in such therapy is often unconscious in origin, the slow methods of psychoanalysis being in a sense by-passed to get this material. It seems to the reviewer that such methods can be fraught with danger in the hands of a beginner. However, the possibilities for research in methods of short psychotherapy, using this and similar methods, are tremendous.

H. W. N.

*Myasthenia Gravis.* By ADALBERTO R. GONÍ, translated by Georgianna Simmons Gittinger. 112 pages; 23.5 × 16 cm. 1946. The Williams & Wilkins Company, Baltimore.

This monograph was originally written in Spanish and received such laudatory reviews that the present publishers, in an attempt to promote the interchange of scientific information between North and South America, requested and obtained permission to translate it into English. The various principals concerned in this task are to be congratulated both for the information contained in this little volume and the high quality of its English reproduction.

Thirteen cases of myasthenia gravis observed by the author are reported with a lucid discussion of the historical development, pathology and symptomatology of this disease. The important rôle that prostigmine has played in increasing our ability to recognize and treat this disorder is emphasized, and ephedrine, potassium and thymic radiation are listed as other helpful therapeutic measures. The author does not feel that the rôle of the thymus gland in causation of the disease has been elucidated sufficiently to warrant routine thymic exploration.

The high quality of this work recommends further investigation and translation of the medical products of our neighbors.

J. Z. B.

*The Diagnosis and Treatment of Pulmonary Tuberculosis.* By MOSES J. STONE, M.D., and PAUL DFAULT, M.D., F.A.C.P., with foreword by HENRY D. CHADWICK, M.D. 325 pages; 20.5 × 14 cm. 1946. Lea & Febiger, Philadelphia. Price, \$3.50.

The authors have furnished the medical student, the house officer and the physician in general practice a concise, non-technical, non-controversial survey of our current knowledge of pulmonary tuberculosis. For these groups of medical men the book will serve as a working manual and a valuable introduction to the study of this important disease.

The plan of the book is to devote short readable chapters to the varied phases of the disease. There is an opening historical sketch of tuberculosis and then a short discussion of the tubercle bacillus. The types of this disease and the clinical features are briefly discussed. The principles of physical diagnosis and its application to tuberculosis are presented and are then followed by a more extensive survey of the principles of the roentgen-ray and its value in pulmonary tuberculosis.

Differential diagnosis is emphasized as it should be in a book which will be used more by the general medical practitioner. Each disease that requires differentiation is given a short thumb-nail sketch.

There is good presentation of collapse therapy, although again necessarily in a brief fashion. Basic principles are stressed. Technic is described and excellent illustrative roentgen-rays accompany the text and enhance its value. Complications of therapy are presented.

Special topics discussed include: tracheo-bronchial tuberculosis; tuberculous laryngitis, enteritis and ano-rectal abscess; and the effect on tuberculosis of complicating syphilis and diabetes. Tuberculosis in industry, social aspects of tuberculosis, tuberculosis and marriage and tuberculosis and pregnancy are all discussed briefly. Case finding surveys and B.C.G. vaccine are presented as factors in prevention.

The foregoing will show the wide range of subject matter covered by the work and the size of the book will indicate how briefly these subjects are discussed.

The point of view is modern, the concepts of the disease are fully up to the latest information. For those to whom it is directed the book is highly recommended.

M. W. J.

### BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*War Stress and Neurotic Illness.* Second Edition. By ABRAM KARDINER, M.D., with the collaboration of HERBERT SPIEGEL, M.D. 428 pages; 21 × 14.5 cm. 1947. Paul B. Hoeber, Inc., New York. Price, \$4.50.

*The Peripheral Circulation in Health and Disease.* A Study in Clinical Science. By ROBERT L. RICHARDS, M.D., Rockefeller Fellow in Medicine. Foreword by J. R. LEARMONTH, C.B.E., Ch.M., F.R.C.S.E. 153 pages; 25.5 × 17.5 cm. 1947. The Williams and Wilkins Company, Baltimore. Price, \$6.00.

*Penicillin in Syphilis.* By JOSEPH EARLE MOORE, M.D. 319 pages; 23.5 × 15.5 cm. 1947. Charles C. Thomas, Springfield, Ill. Price, \$5.00.

- The Significance of the Extracellular Fluid in Clinical Medicine.* From Ernest A. Sommer Memorial Lectures. By L. H. NEWBURGH, M.D., Professor of Clinical Investigation, University of Michigan. 64 pages; 21.5 × 14 cm. 1946. Paggo, Inc., Ann Arbor, Mich. Price, \$1.80.
- Whither Medicine: From Dogma to Science.* By ANTONY FIDLER, M.D., Assoc. Prof. of Medicine, University of Warsaw. 115 pages; 20.5 × 14 cm. 1946. Thomas Nelson and Sons Lt., London, New York. Price, 6/-net.
- X-Ray Diffraction Studies in Biology and Medicine.* By MONA SPIEGEL-ADOLF, M.D., and GEORGE C. HENNY, M.S., M.D. 215 pages; 24 × 15.5 cm. 1947. Grune & Stratton, Inc., New York. Price, \$5.50.
- Fundamentals of Clinical Neurology.* By H. HOUSTON MERRITT, M.D., FRED A. METTLER, M.D., Ph.D., and TRACY JACKSON PUTNAM, M.D. 289 pages; 25.5 × 17 cm. 1947. The Blakiston Company, Philadelphia. Price, \$6.00.
- Medicine in the Changing Order.* Report of the New York Academy of Medicine, Committee on Medicine and the Changing Order. 240 pages; 21.5 × 14 cm. 1947. The Commonwealth Fund, New York. Price, \$2.00.
- Essentials of Endocrinology.* Second Edition, Revised and Enlarged. By ARTHUR GROLLMAN, Ph.D., M.D., F.A.C.P. 644 pages; 24 × 16 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, \$10.00.
- Radical Surgery in Advanced Abdominal Cancer.* By ALEXANDER BRUNSCHWIG, M.D., Professor of Surgery, University of Chicago. 324 pages; 24.5 × 17.5 cm. 1947. The University of Chicago Press, Chicago. Price, \$7.50.
- Handbook of Physiology and Biochemistry.* 39th Edition. By R. J. S. McDOWALL, M.D., D.Sc., Prof. of Physiology, Univ. of London, King's College. 898 pages; 21 × 14.5 cm. 1946. The Blakiston Company, Philadelphia. Price, \$7.00.
- Transactions of the Association of American Physicians.* Fifty-ninth Session. Vol. LIX. 293 pages; 23 × 15.5 cm. 1946. Assoc. American Physicians, Philadelphia.
- Die Hormonversorgung des Foetus.* By Dr. JULES SAMUELS, Amsterdam. 320 pages; 24.5 × 16 cm. 1947. E. J. Brill, Leiden, Holland.
- Formen und Ursachen der Herzhypertrophie bei Lungentuberkulose.* By Professor Dr. W. BERBLINGER, Bern. 183 pages; 23 × 15.5 cm. 1947. Verlag Hans Huber, Bern, Switzerland. Grune & Stratton, sole distributors for the U.S.A. and Canada.
- A Handbook of Commonly Used Drugs.* By MICHEL PIJOAN and CLARK H. YAEGER. 198 pages; 24 × 16 cm. 1947. Charles C. Thomas, Springfield, Ill. Price, \$3.75.
- Functional Cardiovascular Disease.* By MEYER FRIEDMAN, M.D. 266 pages; 24 × 16 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, \$3.00.
- Die Hormonalen Aspekte des Fortpflanzungsprozesses.* By Dr. JULES SAMUELS, Amsterdam. 152 pages; 24.5 × 16 cm. 1946. Holdert & Co. N. V., Amsterdam, Holland.



# COLLEGE NEWS NOTES

## ADDITIONAL LIFE MEMBERS

The College takes pleasure in announcing that the following Fellows have become Life Members, as of the dates cited:

Richard Francis McLaughlin, Burlingame, Calif., March 18, 1947  
Dwight L. Wilbur, San Francisco, Calif., March 21, 1947  
Henry Cook Macatee, Washington, D. C., March 25, 1947  
Abraham S. Rubnitz, Omaha, Nebr., March 26, 1947  
Wm. Miller Dugan, Indianapolis, Ind., March 29, 1947  
Abraham Klein, Brooklyn, N. Y., April 7, 1947  
Saul Solomon, New York, N. Y., April 11, 1947

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## DR. BORTZ TO BE NEXT PRESIDENT OF AMERICAN MEDICAL ASSOCIATION

Following the recent resignation of Dr. Olin West as President-Elect of the American Medical Association, Dr. Edward LeRoy Bortz, F.A.C.P., Philadelphia, Vice President of the Association, succeeded to that office. Dr. Bortz will become President of the Association at its annual meeting in Atlantic City in June.

A Fellow of the American College of Physicians since 1929, Dr. Bortz has been outstandingly active in its work. For a number of years he has served as College Governor for Eastern Pennsylvania, and is now Vice-Chairman of the Board of Governors. He has been Chairman of the Advisory Committee on Postgraduate Courses for the past nine years, and in this position has played an important part in planning the College's very successful program of postgraduate instruction.

Dr. Bortz organized and served as first Chairman of War-Time Graduate Medical Meetings, a program sponsored by the American College of Physicians in which the American College of Surgeons and the American Medical Association joined, which brought leading medical teachers to military installations throughout the country.

Since 1944 Dr. Bortz has been Chairman of the Council on Scientific Assembly of the American Medical Association, and, since 1946, Chairman of its Committee on National Emergency. In Dr. Bortz, its 100th President, the Association will find an enthusiastic and indefatigable worker.

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## A BRIEF REVIEW OF THE CHICAGO ANNUAL SESSION

The Twenty-eighth Annual Session of the College at Chicago, April 28-May 2, 1947, was one of its great annual meetings, and the largest in the history of the organization. 4410 is the gross registration; of this number, 609 were ladies—wives and members of the families of physicians in attendance. The highest gross registration previously was 4,037, Philadelphia, 1946.

The large attendance is attributed to the central meeting place and the exceedingly fine program arranged by President David Barr and General Chairman LeRoy H. Sloan, with the aid of local Chicago committeemen. Still another influence was the great enthusiasm of our Chicago Fellows.

Two hundred and thirty-one new Fellows were inducted at the Convocation, and Masterships were conferred upon four distinguished Fellows, in recognition of their past contributions to the College, personal character, positions of influence and honor,

eminence in practice or in medical research and other attainments in science or in the art of medicine. Those who received Masterships are Dr. George Morris Piersol, Philadelphia, Pa.; Dr. Sydney R. Miller, Baltimore, Md.; Dr. Ernest B. Bradley, Lexington, Ky.; and Dr. John H. Musser, New Orleans, La. Two hundred and seventy physicians were elected to Associateship. One former Fellow was re-instated.

The Technical Exhibit included 102 booths, with 86 separate firms exhibiting. This Exhibit was of high order, with only products relevant to medicine on display by firms who were selected with care by the Committee on Exhibits. Reports from the exhibitors were uniformly gratifying.

Among the unusual items of entertainment was the exclusive showing on the opening night of the play "Harvey" at the Harris Theater, featuring Joe E. Brown. The entire theater was chartered and paid for by College members of Chicago and environs. It was an amusing and excellent presentation, and the College and its members are deeply indebted to the local Committee on Entertainment for a most pleasant evening.

The Ladies' Entertainment Committee provided an exceptionally fine program of entertainment for the visiting women. Their success is the more creditable because more than six hundred visiting women were registered, the largest number ever to attend an Annual Session of the College.

Meeting room facilities were entirely inadequate for the large crowd; the General Sessions meeting place was crowded to overflowing at every session; the panel discussion rooms could not accommodate the large numbers who wished to attend; some of the hospital clinics likewise were filled to capacity, but, by and large, the clinics were not adequately attended, as in previous years. This may, in some measure, be attributed to the very large number of clinics, resulting in wide dispersing of the group, and to the attractiveness of the Morning Lectures which were in session at the same hours. The whole Session is being carefully studied and ways will be sought to improve arrangements in future planning.

The following physicians were, upon recommendation by the Committee on Credentials, elected to Fellowship and Associateship in the College on April 27, 1947, at Chicago. The names of those elected to Fellowship have been given in full capital letters; those elected to Associateship are given in capital and lower case letters.

William W. Abrams, Kansas City, Kan.  
M. VAUN ADAMS, Mobile, Ala.  
Mark Aisner, Boston, Mass.  
LOUIS F. ALBRIGHT, Spring Lake, N. J.  
Hyman Alexander, New York, N. Y.  
Stewart Francis Alexander, Park Ridge, N. J.  
Esta Ross Allen, Clarksburg, W. Va.  
Robin Nail Allin, Madison, Wis.  
LOUIS KATZ ALPERT, Washington, D. C.  
HOWARD LANG ALT, Evanston, Ill.  
John W. A. Althaus, Des Moines, Iowa  
FORREST N. ANDERSON, Van Nuys, Calif.  
Arnold Valenzuela Arms, Kansas City, Mo.  
MYRON AUGUST, Cleveland, Ohio

Robert Earl Beamish, Winnipeg, Man., Can.  
GEORGE OLAF BELL, Boston, Mass.  
LENNOX G. BELL, Winnipeg, Man., Can.  
Solomon Ben-Asher, Jersey City, N. J.  
Morton Emmett Berk, Honolulu, T. H.  
Robert Chambliss Berson, Nashville, Tenn.  
FREDERIC TREMAINE BILLINGS, JR.,  
Nashville, Tenn.  
OSCAR BLITZ, New Orleans, La.  
Malcolm Block, Ann Arbor, Mich.  
Richard A. Bloomfield, Boston, Mass.  
Lester Sylvan Blumenthal, Washington, D. C.  
Milton Edward Bobey, Cleveland, Ohio  
John Lynch Bohan, Galesburg, Ill.  
Frederick Joseph Bradshaw, Jr., Coatesville, Pa.  
LeROY H. BRIGGS, San Francisco, Calif.  
Morris Harold Brodkey, Omaha, Nebr.  
LEWIS H. BRONSTEIN, New York, N. Y.  
Robert Jacob Brochner, M.C., U. S. Army  
Carlton F. Brown, Detroit, Mich.  
Earl Benedict Brown, New York, N. Y.  
John Welch Brown, Madison, Wis.  
Martin Stowell Buehler, Dallas, Tex.  
Victor Bernard Buhler, Kansas City, Mo.

Henry Jacob Bakst, Boston, Mass.  
LEWIS BARBATO, Lakewood, Colo.  
James Henry Barnard, New York, N. Y.  
James Adam Barr, Oakland, Calif.  
Frank Rudolph Barta, Omaha, Nebr.  
Allan Delmage Bass, Syracuse, N. Y.  
John D. Battle, Easton, Pa.  
JULIUS BAUER, Los Angeles, Calif.  
Theodore J. Bauer, U. S. Public Health Service

James Otey Burke, Richmond, Va.  
 OTTO LEO BURTON, M.C., U. S. Navy  
 J. SCOTT BUTTERWORTH, New York,  
 N. Y.  
 MARSHALL PAUL BYERLY, Baltimore, Md.

THOMAS JOHN CARNICELLI, Framing-  
 ham, Mass.

Randolph Armistead Cate, Nashville, Tenn.  
 ASHER S. CHAPMAN, Oyster Bay, N. Y.  
 Louis Cherniack, Winnipeg, Man., Can.  
 Rudolph Chess, Topeka, Kans.  
 George Edward Clark, Jr., Austin, Tex.  
 Raymond S. Clark, West Los Angeles, Calif.  
 Jack Quillian Cleveland, Coral Gables, Fla.  
 Walter Donald Close, Indianapolis, Ind.  
 William Bernard Coen, Springfield, Mass.  
 Charles West Coffen, Portland, Ore.  
 HOWARD C. COGGESHALL, Dallas, Tex.  
 Julian Cohen, Paterson, N. J.  
 THEODORE DAVID COHN, Brooklyn, N. Y.  
 Walter Richard Cook, M.C., U. S. Army  
 Forest Hilton Coulson, Burlington, Iowa  
 Leela Stevens Craig, Berkeley, Calif.  
 A. REYNOLDS CRANE, Philadelphia, Pa.  
 P. THURMAN CRAWFORD, Memphis, Tenn.  
 Robert Clifford Crawford, Roanoke, Va.  
 Harold Roland Cummings, Los Angeles, Calif.

Charles Sprecher Davidson, Boston, Mass.  
 Sidney Davidson, Boynton Beach, Fla.  
 Martin Wheatley Davis, St. Louis, Mo.  
 HOWARD O. DENNIS, Beverly Hills, Calif.  
 CHARLES L. DENTON, M.C., U. S. Navy  
 RURICO SANTIAGO DIAZ-RIVERA, San-  
 turce, P. R.

HERMAN A. DICKEL, Portland, Ore.  
 KARL LAVON DICKENS, Martinsville, Ind.  
 Robert Dickes, Brooklyn, N. Y.  
 FRANK SIGEL DIETRICH, Memphis, Tenn.  
 Donald Thayer Dodge, Philadelphia, Pa.  
 Arthur Leo Donovan, St. John, N. B., Can.  
 THOMAS O. DORRANCE, Bluffton, Ind.  
 Truman Guthred Drake, Jr., St. Louis, Mo.  
 John Frank Drapiewski, Wilkes-Barre, Pa.  
 NORMAN WALTER DREY, St. Louis, Mo.  
 WILLIAM B. DUBLIN, Indianapolis, Ind.  
 JOSEPH L. DUFFY, London, Ont., Can.  
 Thelma Brumfield Dunn, Bethesda, Md.  
 Donald Alphaeus Dupler, Philadelphia, Pa.  
 Edwin Mather Duvall, Long Beach, Calif.

Donald Thomas Edmeades, Pasadena, Calif.  
 Stanley Russell Edwards, Los Angeles, Calif.  
 MAURICE ELIASER, JR., San Francisco,  
 Calif.

John Lawson Elliott, Savannah, Ga.  
 George Bache Emory, Jr., Morristown, N. J.  
 SAMUEL EPSTEIN, Brooklyn, N. Y.  
 Silas McAfee Evans, Milwaukee, Wis.  
 WILLIAM DUSTIN EVANS, North Holly-  
 wood, Calif.

STANLEY C. W. FAHLSTROM, Chicago, Ill.  
 William Feiring, Richmond Hill, N. Y.  
 JOHN LUMICE FERRY, Whiting, Ind.  
 Jerome Kearney Fisher, New York, N. Y.

Jarrett Harter Folley, Hanover, N. H.  
 RAOUL FOURNIER, Mexico, D. F.  
 ROBERTO FRANCISCO AZIZE, San Juan,  
 P. R.

Ludwig Frank, Charleston, W. Va.  
 Joseph Jerome Frankel, Hines, Ill.  
 Leo Fred, Los Angeles, Calif.  
 ELLIS B. FREILICH, Chicago, Ill.  
 ISRAEL SIMON FREIMAN, New York, N. Y.  
 Joseph David Friedland, Denver, Colo.  
 Burt Friedman, Memphis, Tenn.  
 Robert Howard Furman, Nashville, Tenn.

Raymond Masson Galt, Chicago, Ill.  
 MARK W. GARRY, Worthington, Ohio  
 Maxwell L. Gelfand, New York, N. Y.  
 John Otto Gibbs, San Francisco, Calif.  
 Frederick Lemuel Giles, Honolulu, T. H.  
 DELMAR R. GILLESPIE, St. Paul, Minn.  
 DANIEL A. GLOMSET, Des Moines, Iowa  
 Bernard I. Goldberg, Newton Center, Mass.  
 Alfred Golden, Memphis, Tenn.  
 FREDERICK GOLDMAN, Cincinnati, Ohio  
 Abraham Mitchell Gottlieb, Detroit, Mich.  
 John Ruskin Graham, Boston, Mass.  
 Louis W. Granirer, Broad Channel, N. Y.  
 Robert Coleman Grauer, Pittsburgh, Pa.  
 OTTO EARLE GRAY, Chicago, Ill.  
 FREDERICK C. GREAVES, M.C., U. S. Navy  
 DANIEL MARIE GREEN, Seattle, Wash.  
 Arthur Morton Greene, Omaha, Nebr.  
 Tibor Jack Greenwalt, Milwaukee, Wis.  
 Alton Claren Grorud, Bismarek, N. D.  
 PAUL GROSS, Glenshaw, Pa.  
 John Lippincott Guerrant, Charlottesville, Va.  
 WILLIAM A. GUEST, Ottawa, Ont., Can.

Paul Oonk Hagemann, St. Louis, Mo.  
 SNOWDEN C. HALL, JR., Danville, Va.  
 WENDELL C. HALL, Hartford, Conn.  
 WILLIAM E. B. HALL, Port Huron, Mich.  
 BENGT L. K. HAMILTON, Chicago, Ill.  
 PERCY G. HAMLIN, Santa Barbara, Calif.  
 Benjamin Marvin Hand, Philadelphia, Pa.  
 Gordon Middleton Hankins, Birmingham, Ala.  
 Clifford Henry Hansen, Omaha, Nebr.  
 SAMUEL HANTMAN, Cleveland, Ohio  
 John Thomas Hardesty, Long Beach, Calif.  
 Edward O'Neil Harper, Cleveland, Ohio  
 A. McGEHEE HARVEY, Baltimore, Md.  
 Robert Joseph Hasterlik, Evanston, Ill.  
 James West Haviland, Seattle, Wash.  
 RALPH O. HAYDEN, St. Charles, Mo.  
 Jack Murray Hayes, Omaha, Nebr.  
 GEORGE A. HELLMUTH, Chicago, Ill.  
 John Burnham Hibbs, Uniontown, Pa.  
 Alton Reginald Higgins, M.C., U. S. Navy  
 John Stephen Hirschboeck, Milwaukee, Wis.  
 Harold Lester Hirsh, Washington, D. C.  
 Elliot Hochstein, New York, N. Y.  
 Horace Hayden Hodges, Philadelphia, Pa.  
 CORRIN H. HODGSON, Rochester, Minn.  
 HERMAN S. HOFFMAN, Washington, D. C.  
 PAUL HOGG, Newport News, Va.  
 William Henry Hollinshead, Jr., St. Paul, Minn.  
 Edward Estis Holloway, Philadelphia, Pa.

JOE EDWARD HOLOUBEK, Shreveport, La.  
 JESSE MORRIS HORN, Dallas, Tex.  
 Frederic Bernard House, Ann Arbor, Mich.  
 Arnold Beverley Houston, Winnipeg, Man., Can.  
 JOSEPH F. HUGHES, Philadelphia, Pa.  
 John Scott Hunt, Lexington, Ky.  
 ALLEN E. HUSSAR, Los Angeles, Calif.  
 Laurence Mortimer Hutner, Beverly Hills, Calif.

Edwin Newton Irons, Chicago, Ill.  
 Harris Isbell, U. S. Public Health Service  
 Emil Mark Isberg, Miami Beach, Fla.  
 Lionel Mortimer Ives, Northampton, Mass.

Harry George Jacobi, New York, N. Y.  
 Eugene C. Jacobs, M.C., U. S. Army  
 James S. L. Jacobs, Madison, Wis.  
 Leif Yngve Jacobsen, New York, N. Y.  
 Leon Orris Jacobson, Chicago, Ill.  
 Richard Henry Jacques, Columbus, Ohio  
 Stephen Lee Johnson, Evansville, Ind.  
 GEORGE MILLER JONES, Dallas, Tex.  
 Nathaniel Jones, Jacksonville, Fla.

WILLIAM KAUFMANN, Northampton, Mass.  
 Edvard John Keegan, Oneonta, N. Y.  
 Mavis Parrott Kelsey, Rochester, Minn.  
 Saul Rosenthal Kelson, New York, N. Y.  
 Richard Joseph Kennedy, New York, N. Y.  
 Samuel Theodore Killian, Syracuse, N. Y.  
 Harry Edward King, Dayton, Ohio  
 MILTON KISSIN, New York, N. Y.  
 MARGARET S. KLAPPER, Birmingham, Ala.  
 Anna Place Klemmer, Lancaster, Pa.  
 Harry Fitch Klinefelter, Jr., Baltimore, Md.  
 Max Koenigsberg, Charleston, W. Va.  
 Jerome Kotleroff, M.C., U. S. Navy  
 Frederic A. Kramer, St. Louis, Mo.  
 MILTON LURIE KRAMER, New York, N. Y.  
 Newton Krumdieck, Cambridge, N. Y.  
 Paul Kunkel, Newington, Conn.

Alfred Charles LaBocchetta, Philadelphia, Pa.  
 EDWIN LEVER LAME, Philadelphia, Pa.  
 John Tarlton Lane, Hines, Ill.  
 Jack Damgaard Lange, Los Altos, Calif.  
 Paul Harry Langner, Jr., Drexel Hill, Pa.  
 HOWARD JAMES LEE, Milwaukee, Wis.  
 SIDNEY LEIBOWITZ, New York, N. Y.  
 George C. Leiner, New York, N. Y.  
 Santino Joseph Lerro, M.C., U. S. Army  
 C. Ralph Letteer, San Antonio, Tex.  
 Stanley Leon Levin, Des Moines, Iowa  
 Harry Samuel Levine, Brooklyn, N. Y.  
 Irving Milton Levitas, Westwood, N. J.  
 John Albert Lewis, London, Ont, Can.  
 ALAN ALBERT LIEBERMAN, Elgin, Ill.  
 ROBERT SAMUEL LIGGETT, Denver, Colo.  
 Merlyn Carl Fred Lindert, Milwaukee, Wis.  
 BRUCE C. LOCKWOOD, Detroit, Mich.  
 Elmer A. Lodmell, M.C., U. S. Army  
 Lenier Arthur Lodmell, Portland, Ore.  
 OLIVER WILLISON LOHR, Saginaw, Mich.  
 ESMOND RAY LONG, Philadelphia, Pa.  
 JULIAN SAX LONG, Wilkes-Barre, Pa.  
 Monroe Franklin Ley, Los Angeles, Calif.  
 PASCAL F. LUCCHESI, Philadelphia, Pa.

M. Gulden Mackmull, Philadelphia, Pa.  
 JOHN W. MACLEOD, Winnipeg, Man., Can.  
 FREDERICK W. MADISON, Milwaukee, Wis.  
 Francis Roxby Manlove, Philadelphia, Pa.  
 GEORGE E. MARK, JR., Philadelphia, Pa.  
 Casper Markel, Denver, Colo.  
 Elwood W. Mason, Milwaukee, Wis.  
 Porter Kahn Mason, Dallas, Tex.  
 Edgar Frank Mauer, Los Angeles, Calif.  
 Ralph Whiteman Mays, Philadelphia, Pa.  
 Oscar Clarence McCarn, Birmingham, Ala.  
 Florence S. McConney, Toronto, Ont., Can.  
 FRANCIS E. McDONOUGH, Boston, Mass.  
 GEORGE C. McEACHERN, Forest Hills, N. Y.  
 JAMES WARRIE McELROY, Memphis, Tenn.  
 James Marshall McFadden, La Fayette, Ind.  
 SYLVESTER MCGINN, Boston, Mass.  
 CHRISTOPHER JOHN McLOUGHLIN, Atlanta, Ga.  
 ROBERT LINDSAY McMILLAN, Winston-Salem, N. C.  
 LEO JOSEPH MEIENBERG, Portland, Ore.  
 CHARLES LeROY MENGEL, Allentown, Pa.  
 SAMUEL R. MERCER, Ft. Wayne, Ind.  
 Wallace Alfred Merritt, Rochester, Minn.  
 MURLIN P. MERRYMAN, Rapid City, S. D.  
 WASHINGTON MERSCHER, Clifton Springs, N. Y.  
 LOUIS A. MILKMAN, Scranton, Pa.  
 Ben Neely Miller, Columbia, S. C.  
 C. Joseph Miller, Philadelphia, Pa.  
 Harold Edmund Miller, Minneapolis, Minn.  
 James Rex Miller, Salt Lake City, Utah  
 Samuel Irving Miller, Jr., Houston, Tex.  
 James Monroe, Ray Brook, N. Y.  
 Franklin Bernard Moosnick, Lexington, Ky.  
 Leo David Moss, Olean, N. Y.  
 GEORGE E. MOUNTAIN, Des Moines, Iowa  
 Fred Howenstine Mowrey, M.C., U. S. Army  
 S. Edwin Muller, Baltimore, Md.  
 Eusebius Jerome Murphy, New York, N. Y.  
 James Patrick Murphy, St. Louis, Mo.

Joseph Britton Neighbors, Jr., Athens, Ga.  
 Russell A. Nelson, Baltimore, Md.  
 Harold Nicholas Neu, Omaha, Nebr.  
 Louis George Neudorff, St. Joseph, Mo.  
 Edward Nichols, Hartford, Conn.  
 David Niemetz, Beverly Hills, Calif.  
 Bernard Mallon Norcross, Buffalo, N. Y.  
 Meyer Notkin, Paterson, N. J.  
 Bernard Emilio Nunez, Washington, D. C.  
 Harvey Eleazar Nussbaum, Newark, N. J.

James Nester O'Brien, Harrisburg, Pa.  
 Nicholas Rosario Occhino, Johnson City, N. Y.  
 William Frazier Owen, Jr., Utica, N. Y.

HENRY PACKER, Memphis, Tenn.  
 David Harold Paley, New York, N. Y.  
 Arthur Seymour Parker, Jr., Boston, Mass.  
 George Mason Parker, Peoria, Ill.  
 Allen Almon Parry, Madison, N. J.  
 Marion Lofton Patton, Memphis, Tenn.  
 Bruno Joseph Peters, Milwaukee, Wis.  
 Clifford Henry Peters, Bismarck, N. D.

LESTER MARSHALL PETRIE, Decatur, Ga.  
 MORTON M. PINCKNEY, Richmond, Va.  
 ROBERT FRANKLIN PITTS, Syracuse, N. Y.  
 Herbert William Pohle, Shorewood, Wis.  
 EVERETT BLANKS POOLE, Greenville, S. C.  
 Lester Junior Pope, M. C., U. S. Navy  
 ROSS JOSEPH PORRITT, Pontiac, Mich.  
 Robert Potashnick, St. Louis, Mo.  
 GEORGE M. POWELL, M. C., U. S. Army  
 WALTER SCOTT PRIEST, Chicago, Ill.  
 Everett William Probst, Arlington, N. J.  
 James Paul Proudfit, Washington, Pa.  
 LAWRENCE E. PUTNAM, Washington, D. C.

Edwin Danford Quick, Riverside, Calif.

Edward Cowell Raffensperger, Philadelphia, Pa.  
 Theron Grant Randolph, Chicago, Ill.  
 CHARLES DICKENS REECE, Houston, Tex.  
 William Anton Henry Rettberg, Denver, Colo.  
 JAMES RISLEY REULING, Bayside, N. Y.  
 SAMUEL T. R. REVELL, JR., Baltimore, Md.  
 Frank Walker Reynolds, Baltimore, Md.  
 STEPHEN REYNOLDS, Santa Monica, Calif.  
 Norman Bridge Roberg, Chicago, Ill.  
 Charles Purcell Roberts, Atlanta, Ga.  
 Edward Pier Roemer, Madison, Wis.  
 John David Roger, Ottawa, Ont., Can.  
 Joseph Handley Rogers, Gadsden, Ala.  
 MONROE J. ROMANSKY, Washington, D. C.  
 MARIAN WILKINS ROPES, Boston, Mass.  
 FRANCIS F. ROSENBAUM, Milwaukee, Wis.  
 Nathaniel Edward Rossett, Memphis, Tenn.  
 George Parke Rouse, Jr., Philadelphia, Pa.  
 Jacob Rubin, Savannah, Ga.  
 JOHN M. RUMSEY, San Diego, Calif.  
 BENJAMIN HUGER RUTLEDGE, Baltimore, Md.

ADOLPH LOUIS SAHS, Iowa City, Iowa  
 Byron Douglas St. John, Port Washington, N. Y.  
 MARIO SALAZAR MALLEN, Mexico, D. F.  
 Louis Michael Sales, Indianapolis, Ind.  
 Pierre Joseph Salmon, Brooklyn, N. Y.  
 Joseph Frank Sandella, New Brunswick, N. J.  
 WILLIAM SAPHIR, Chicago, Ill.  
 Irvin Sauber, Baltimore, Md.  
 MAXWELL SCARF, Philadelphia, Pa.  
 LOUIS A. SCARPELLINO, Kansas City, Mo.  
 WALTER LOUIS SCHAFER, Wichita, Kans.  
 Gerhard L. Scherk, New York, N. Y.  
 Harold Saul Schiro, Cincinnati, Ohio  
 Emanuel Barnett Schoenbach, Baltimore, Md.  
 Jack Spalding Schroder, Atlanta, Ga.  
 John Matthai Scott, Baltimore, Md.  
 THAD P. SEARS, Fort Logan, Colo.  
 George Joseph Seibold, Houston, Tex.  
 Laurence A. Senseman, Saylesville, R. I.  
 WILLIAM PRIOR SHELTON, Dallas, Tex.  
 ROYAL V. SHERMAN, Red Wing, Minn.  
 WILLIAM B. SHERMAN, New York, N. Y.  
 RICHARD M. SHICK, Rochester, Minn.  
 Harold Michael Shorr, New York, N. Y.  
 LOUIS A. SIERACKI, Norwood, Mass.  
 Emanuel Sigoloff, Los Angeles, Calif.  
 William W. Simpson, Vancouver, B. C., Can.

Raymond Edwin Sinalley, Billings, Mont.  
 Leon Samuel Smelo, Birmingham, Ala.  
 Arthur Lawrence Smith, Jr., Lincoln, Nebr.  
 CHARLES W. SMITH, Harrisburg, Pa.  
 KENDRICK A. SMITH, Los Angeles, Calif.  
 ROBERT L. SMITH, JR., San Francisco, Calif.  
 ROY KENNETH SMITH, Masan, Korea  
 Robert Moses Sonneborn, Wheeling, W. Va.  
 SAMUEL SOSKIN, Chicago, Ill.  
 Hamilton Southworth, New York, N. Y.  
 MITCHELL A. SPELLBERG, Chicago, Ill.  
 Helmuth S. E. Sprinz, M. C., U. S. Army  
 HARRY ARTHUR STECKEL, Syracuse, N. Y.  
 EDSON HUN STEELE, Los Angeles, Calif.  
 Hugh Henderson Steelc, Detroit, Mich.  
 William Brooks Steen, Tucson, Ariz.  
 Max Hyman Stein, Brooklyn, N. Y.  
 William Stein, Milwaukee, Wis.  
 Robert Leo Stern, Beverly Hills, Calif.  
 Myer Harold Stolar, Washington, D. C.  
 Samuel Frederick Strain, Memphis, Tenn.  
 Elias Strauss, Dallas, Tex.  
 John Christian Sullivan, Washington, D. C.  
 William Richard Sulman, Hazleton, Pa.  
 RALPH M. SUSSMAN, New York, N. Y.  
 Daniel Mason Swan, Quincy, Mass.  
 CLIFFORD A. SWANSON, M. C., U. S. Navy

Hugh Tatlock, Northampton, Mass.  
 Solomon Taubin, Yonkers, N. Y.  
 Elizabeth Alice Taylor, Fort Worth, Tex.  
 JAMES TESLER, Brooklyn, N. Y.  
 KENT H. THAYER, Phoenix, Ariz.  
 CHARLES E. THOMPSON, Memphis, Tenn.  
 John Kenneth Thompson, Fort Smith, Ark.  
 David Highbaugh Thurman, Louisville, Ky.  
 William Joseph Tighe, San Diego, Calif.  
 RALPH WALDO TRIMMER, Oak Park, Ill.  
 Henry St. George Tucker, Jr., Richmond, Va.  
 Frederic Tudor, Milton, Mass.  
 John Edward Tysell, Chicago, Ill.

Milton Harmond Uhley, Chicago, Ill.  
 Dan Lowell Urschel, Mentone, Ind.

Albert Vander Kloot, Chicago, Ill.  
 RAYMOND VANDER MEER, New York; N. Y.  
 Frank Walter Van Kirk, Jr., Janesville, Wis.  
 Vernon Van Zandt, Los Angeles, Calif.  
 HARRY VESELL, New York, N. Y.  
 Karl Otto Von Hagen, Los Angeles, Calif.  
 WILLIAM G. von STEIN, New York, N. Y.

William Wayne Waddell, Beatrice, Nebr.  
 Richard Clarke Wadsworth, Bangor, Maine  
 Joseph Adam Wagner, Philadelphia, Pa.  
 Thomas Angell Warltin, Natick, Mass.  
 EDGAR WAYBURN, San Francisco, Calif.  
 HARRY F. WECHSLER, New York, N. Y.  
 Clarence Kraus Weil, Montgomery, Ala.  
 OLIVER WILLIAM WELCH, Fairfield, Ala.  
 Louis Gordon Welt, Willimantic, Conn.  
 Robert E. Westmoreland, Indianapolis, Ind.  
 Robert LaFayette Whipple, Jr., Atlanta, Ga.  
 Walter Kellogg Whitehead, Detroit, Mich.

MEYER R. WHITEHILL, Norfolk, Va.  
 E. Gale Whiting, Berkeley, Calif.  
 ROGER SHERMAN WHITNEY, Colorado  
 Springs, Colo.  
 Ira Wickner, Newburgh, N. Y.  
 James MacLean Wilkie, Madison, Wis.  
 JOHN POWELL WILLIAMS, Richmond, Va.  
 RUSSELL D. WILLIAMS, Monterey, Calif.  
 DONALD M. WILLSON, Milwaukee, Wis.

HENRY LUDWIG WOLLENWEBER, Baltimore, Md.  
 ROBERT MAX WOODS, Los Angeles, Calif.  
 RAYMOND J. WYRENS, Omaha, Nebr.  
 Samuel Zelman, Topeka, Kans.  
 BRUCE ZIMMERMAN, Seattle, Wash.  
 SOLOMON L. ZIMMERMAN, Columbia, S. C.  
 Horace Helmut Zinneman, Lincoln, Nebr.

### SPECIALTY BOARD EXAMINATIONS

American Board of Pathology; Robert A. Moore, M.D., Secretary, Euclid Ave. and Kingshighway, St. Louis 10, Mo. Examination, June 5-6, 1947 (note change in date from June 3-4, March issue), Philadelphia, Pa.; October 24-25, Chicago, Ill.

American Board of Internal Medicine; William A. Werrell, M.D., Assistant Secretary-Treasurer, 1 W. Main St., Madison 3, Wis. Examination in various cities, October 20, 1947 (closing date of acceptance of applications, June 1).

### UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE REORGANIZES DEPARTMENT OF MEDICINE

Effective July 1, 1947, Dr. O. H. Perry Pepper, F.A.C.P., will relinquish the headship of the Department of Medicine of the University of Pennsylvania School of Medicine. Dr. Pepper will continue his activities as Professor of Medicine and as a member of the medical staff of the Hospital of the University of Pennsylvania. Dr. Francis C. Wood, F.A.C.P., whose promotion from Assistant Professor to Professor of Medicine will take effect on the above date, will succeed Dr. Pepper as head of the department.

In announcing the reorganization of the department, President George W. McClelland stated, "Modern advances in all branches of medicine are so great that no one man can be expert in all. A balanced department now has to divide responsibility in accordance with the gifts of all the members of its staff. Accordingly . . . the University has made four new appointments to full professorships of medicine." In addition to Dr. Wood's appointment, Drs. T. Grier Miller, F.A.C.P., Truman G. Schnabel, F.A.C.P., and Charles C. Wolferth, F.A.C.P., presently Professors of Clinical Medicine, will become Professors of Medicine on July 1.

Dr. Pepper, a former President and Regent of the College, succeeded the late Dr. Alfred Stengel, M.A.C.P., as head of the Department of Medicine. During the war years Dr. Pepper not only maintained his obligations in the Medical School and Hospital of the University of Pennsylvania, but also served as a Consultant to the Secretary of War and as a member of various Army Committees and Boards, as Consultant to the Office of Scientific Research and Development, and as Chairman of the Committee on Medicine of the National Research Council and as member of a number of N.R.C. Committees and Sub-committees.

Dr. Wood, a graduate of Princeton University and the University of Pennsylvania School of Medicine, has served in the Department of Medicine and in the Edward B. Robinette Foundation, of which Dr. Wolferth is Director, since 1928. During World War II Dr. Wood was a member and, subsequently, Chief of the Medical Section of the 20th General Hospital, the University Hospital's unit which was located in Assam. Dr. Wood is a member of the Society for Clinical Investigation, the Peripatetic Society, American Heart Association, American Medical Association, College of Physicians of Philadelphia, American Clinical and Climatological Association, and has been a Fellow of the College since 1938.

Dr. Miller, a Regent and the Marshal of the College, is also President of the

Philadelphia County Medical Society, and has been elected the next President of the College of Physicians of Philadelphia and American Clinical and Climatological Association. Dr. Schnabel, a representative of the College in the American Board of Internal Medicine, is head of the University's medical service in the Philadelphia General Hospital.

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#### A.C.P. POSTGRADUATE COURSES

At the time of writing, somewhat more than 500 physicians have enrolled in the Spring, 1947, Postgraduate Courses, all of which have proved the continued popularity of this activity of the College. A full analysis of the enrollments in these courses will be published in the June issue, as well as the proposed schedule of courses for the Autumn of 1947. The Advisory Committee on Postgraduate Courses and the Committee on Educational Policy held a joint meeting during the Annual Session in Chicago and their report will also be published in the June issue.

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#### REPORT ON NEBRASKA REGIONAL MEETING, MARCH 29, 1947

A Regional Meeting of the American College of Physicians was held in Omaha, Nebraska, March 29, 1947. Of the 55 Nebraska members, 49 were in attendance at the Meeting and the Dinner. The total attendance was 70 physicians.

The Scientific Session was excellent. The cocktail hour, followed by dinner, was conducted in the evening, giving a real opportunity for the members to become better acquainted with one another. The speakers in the evening included Dr. H. C. Lueth, F.A.C.P., Dr. C. M. Wilhelmj, and Dr. Ralph A. Kinsella, F.A.C.P., College Governor for Missouri. The Nebraska members voted unanimously to hold a similar meeting in Lincoln in the Autumn.

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John Everett Gordon, M.D., F.A.C.P., Boston, Mass., formerly Colonel (MC), A.U.S., has been awarded the Legion of Merit and the U. S. Typhus Commission Medal. The effectiveness of Dr. Gordon's efforts as Chief of the Preventive Medicine Division, Office of the Surgeon, Headquarters, European Theater of Operations, in prevention of epidemics of communicable diseases, and particularly in checking the spread of typhus, is cited.

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Dr. Monroe J. Romansky, F.A.C.P., Washington, D. C., has been awarded the Legion of Merit for the development of "technics for administration of penicillin . . . saving lives and alleviating pain and suffering," while a medical officer in the Army of the United States. Dr. Romansky retired from the service in July, 1946, with rank of Major.

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Through the courtesy of the author, the College Library has received a copy of the New 2nd Edition of "Essentials of Endocrinology," by Arthur Grollman, Ph.D., M.D., F.A.C.P., published by J. B. Lippincott Company, Philadelphia, 1947.

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Dr. Tinsley R. Harrison, F.A.C.P., Dallas, Tex., and Dr. Thomas P. Findley, F.A.C.P., New Orleans, La., have been elected President and Secretary and Treasurer, respectively, of the Southern Society for Clinical Research.

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#### CALIFORNIA SOCIETY OF INTERNAL MEDICINE

The California Society of Internal Medicine, 2180 Washington St., San Francisco, was organized in July, 1946. Its membership, now 250, is open to physicians who

are U. S. citizens, residents of and licensed to practice in California, who are qualified as specialists in internal medicine.

The purposes of the Society are stated to be: "1. To unite the qualified internists of the state in a representative organization for the furtherance of the practice of Internal Medicine. 2. To study the scientific, economic, social and political aspects of medicine in order to secure and maintain the highest standards of practice in Internal Medicine. 3. To coöperate with other organizations of like purpose."

The governing body is a Council, composed of the President, Vice-President, Secretary-Treasurer, and six other members of the Society. W. L. Bender, M.D., San Francisco, is President; and Donald E. Griggs, M.D., F.A.C.P., Los Angeles, is Vice-President. C. Kelly Canelo, M.D., F.A.C.P., San Jose, John C. Schlappi, M.D., F.A.C.P., San Diego, Howard F. West, M.D., F.A.C.P., Los Angeles, and Frank B. Reardan, M.D. (Associate), are also members of the Council.

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#### FORT LOGAN VETERANS ADMINISTRATION HOSPITAL INITIATES INTERESTING POSTGRADUATE PLAN

Dr. J. Shirley Sweeney, F.A.C.P., Manager of the Veterans Administration Hospital at Fort Logan, Colorado, recently announced a plan to stimulate residents and permanent staff members by engaging a series of outstanding authorities from various parts of the country to present lectures, ward rounds and demonstrations at the Hospital.

The first guest speaker was Dr. Elliott P. Joslin, F.A.C.P., Boston, whose program on March 2-3 included ward rounds for the first half day; an afternoon devoted to lectures to residents and permanent staff members; an evening for an address to the public in the local hospital theater; a morning of lectures to the medical students and faculty of the University of Colorado School of Medicine; and the second evening devoted to an address before the Denver County Medical Society in the station theater.

Others on the invitation list include Dr. William D. Stroud, F.A.C.P., Philadelphia, and Dr. Philip S. Hench, F.A.C.P., of the Mayo Foundation. During the coming summer numerous other guest speakers, including Dr. Max Peet, Dr. Louis H. Newburgh, F.A.C.P., and Dr. Jonathan Meakins, F.A.C.P., are scheduled.

The Fort Logan Veterans Administration Hospital is a Dean's Committee Hospital. Dr. Ward Darley, F.A.C.P., Dean of the University of Colorado School of Medicine, is chairman of the Committee.

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#### POSTGRADUATE MEDICAL INSTRUCTION, NEW YORK STATE

An interesting program is described in "Postgraduate Medical Education, Course Outline Book, 1946-47," published by the Council Committee on Public Health and Education of the Medical Society of the State of New York. Coöperating with the Society in planning the lectures and arranging for lecturers are the State Departments of Health and Labor, the Dental Society of the State of New York, as well as other organizations.

Lectures, courses of lectures, and "Teaching Days," a term used to describe an afternoon and evening program of clinics, demonstrations and lectures, are made available to county medical societies, hospital staffs and other medical groups without charge. Honoraria for speakers are provided by the State Department of Health; travel expense, by the State Society.

The list of offerings, revised annually, covers a wide range of medical topics, under the following headings: Allergy, Bacteriology, Cancer, Chemotherapy, Dentistry, Dermatology, Industrial Health, General Medicine, Gynecology, Neurology,



Neuropsychiatry, Obstetrics, Ophthalmology, Orthopedics and Orthopedic Surgery, Otolaryngology, Pediatrics, Physical Medicine, Plasma Therapy, Proctology, Psychiatry, Public Health and Preventive Medicine, Rheumatic Fever and Heart Disease, Surgery, Syphilis, Tropical Diseases. The detailed list of courses and topics contains some 90 subjects.

A number of the courses have been arranged by Fellows of the College: Allergy, by Dr. Robert A. Cooke, F.A.C.P., New York; courses in Arteriosclerosis and Aging, Heart Disease, and Clinical Aspects of Vascular Disorders, by Dr. Clarence E. de la Chapelle, F.A.C.P., New York; Treatment of Common Diseases, by Dr. Clayton W. Greene, F.A.C.P., Buffalo; Diseases of the Chest, by Dr. J. Burns Amberson, F.A.C.P., New York; Courses in Gastroenterology, General Medicine, and Hemorrhage, by Dr. Albert F. R. Andresen, F.A.C.P., Brooklyn; other courses in General Medicine, by Drs. Walter W. Palmer, F.A.C.P., and Linn J. Boyd, F.A.C.P., New York, William Dock, F.A.C.P., Brooklyn, William S. McCann, F.A.C.P., Rochester, E. C. Reifenshtein, Sr., F.A.C.P., Syracuse; Hypertension, by Dr. Herman O. Mosenthal, F.A.C.P., New York; Kidney Diseases, by Dr. William Goldring, F.A.C.P., New York; Neuropsychiatric Aspects of Illness, by Dr. S. Bernard Wortis, F.A.C.P., New York.

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#### CUBA NOW REPRESENTED BY ITS OWN GOVERNOR IN THE COLLEGE

At the Annual Business Meeting of the American College of Physicians at Chicago, Ill., May 1, 1947, Dr. José J. Centurión, F.A.C.P., Havana, was elected as College Governor for Cuba. Heretofore, Cuba and the State of Florida were united as one territory, with Dr. T. Z. Cason, F.A.C.P., of Jacksonville, Fla., the Governor for both areas. Now Cuba becomes a separate unit with its own Governor.

Dr. Centurión has been a Fellow of the College since 1941. He graduated from the University of Havana Faculty of Medicine in 1918, and for several years has been Professor of Clinical Medicine at his Alma Mater, and Head of the Medical Ward at the Hospital Nacional General, Calixto Garcia. He specializes in Internal Medicine and Cardiology.

At present there are twelve Fellows of the College in Cuba.

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#### RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to April 14, 1947 inclusive).

James B. Anderson, Richmond, Va. (Lt. Col., MC, USA)  
 Kelso A. Carroll, Pittsburgh, Pa. (Col., MC, AUS)  
 S. Douglas Craig, Winston-Salem, N. C. (Surgeon, USPHS(R))  
 John M. Cruikshank, Nassau, Bahamas, (Flight-Lt., RCAF)  
 John M. McCants, Chester Co., S. C. (Capt., MC, USN)  
 Jerome F. Smith, San Diego, Calif. (Comdr., MC, USN)  
 William W. Wickersham, Philadelphia, Pa. (Capt., MC, USN)

# ANNALS OF INTERNAL MEDICINE

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## LIVER FUNCTION IN HEPATITIS \*

By C. J. WATSON, F.A.C.P., and F. W. HOFFBAUER,  
*Minneapolis, Minnesota*

THE effective morbidity incidence of hepatitis during the war was very great, due not only to the large number of individuals affected but also to the long period of disability. Considerable evidence has been obtained that complete bed rest early in the course of the disease is likely to result in a shorter and milder illness with fewer residual abnormalities.<sup>1, 2, 3</sup> It has also been reasonably well established that to return to physical activity before adequate subsidence of the disease is to invite a relapse which may be more severe than the initial attack.<sup>1, 3</sup> One of the main problems, therefore, was to detect the disease in its incipient stage and to be able to recognize when it was reasonably safe for the individual to resume normal activity with a minimal danger of relapse. The considerable incidence of hepatitis without tangible jaundice<sup>3</sup> has, of course, constituted a very important facet of this whole problem. In addition, the differential diagnosis of jaundice, especially in cases of sporadic type, has emphasized the need of a thorough study of liver function. It has become increasingly evident that such a study must be of composite type if one is to expect any considerable degree of accuracy, either in the differential diagnosis of jaundice or in the detection of latent or residual hepatic injury. Single tests are likely to prove misleading because of remarkable variation from case to case. Examples of this will be discussed subsequently.

The discussion which follows is based upon the clinical and laboratory study of 70 cases of hepatitis, including 21 cases of chronic hepatitis with varying degrees of hepatic cirrhosis. Some of these have been considered in detail elsewhere.<sup>4</sup> The discussion is also based in part upon observations by one of us (C. J. W.†) on many cases of hepatitis in various Army Hospitals, especially the Schick General Hospital at Clinton, Iowa.

\* Clinical lecture presented in part at the meeting of the American College of Physicians, Philadelphia, May 15, 1946. Aided by grants from the Hormel Research Foundation and the Medical Research Fund of the Graduate School of the University of Minnesota.

From the Department of Medicine, University of Minnesota Hospital, Minneapolis, Minnesota.

† Civilian Consultant in Hepatic Diseases to the Secretary of War.

In considering liver functional disturbances, whether in hepatitis or in any other hepatic disease, it is helpful to keep in mind the three functioning units of the liver, namely (1) hepatocellular, (2) cholangiolar, (3) reticulo-endothelial. The available laboratory procedures permit one to gain information about the function of the first two only. While there can be no doubt that the Kupffer cells are often seriously affected in hepatitis, there is at present no means by which one may assay their function or determine the degree of injury which they may have sustained.

The term "cholangiolar" refers especially to what has also been spoken of as the intermediary portion<sup>8</sup> of the intrahepatic biliary tract including the ampullae of the bile capillaries at the periphery of the liver lobule, as shown in figure 1 which has been redrawn from an illustration in Eppinger's

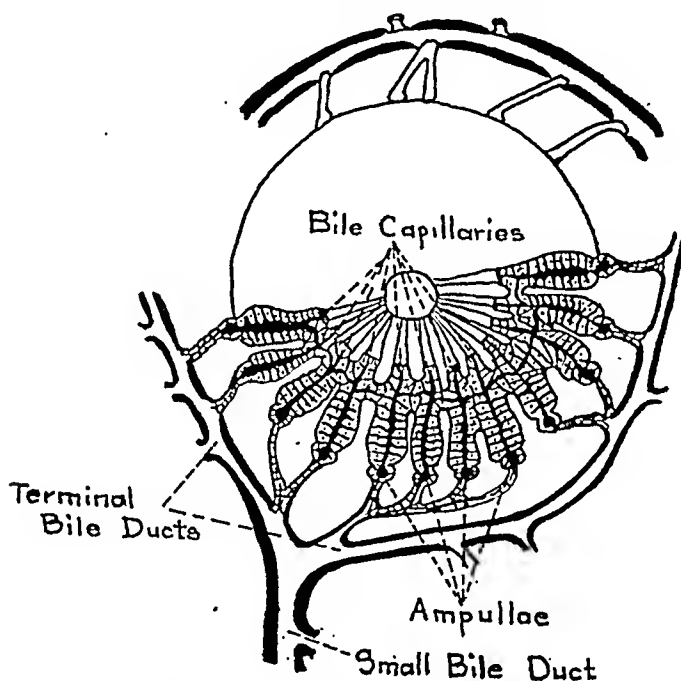


FIG. 1. Schematic drawing of the intrahepatic bile duct system. Redrawn from Eppinger.<sup>5</sup> The term cholangiole, as used in the text, refers to the ampullae of the bile capillaries, the terminal bile ducts, and their connections.

"Diseases of the Liver".<sup>5</sup> There is considerable evidence that these ampullae are especially vulnerable to injury or increased pressure, in fact, Aschoff has referred to them as the "Achilles heel of the biliary tract."<sup>6</sup> The functions listed in table 1 are believed to relate especially to hepatocellular or cholangiolar function as indicated.

It is seen in table 1 that an increase of the delayed, or indirect reacting serum bilirubin is related to hepatocellular functional disturbances, while an increase of the 1' or prompt reacting type is thought to be an evidence of cholangiolar abnormality. This, together with some of the other items listed in table 1, will be discussed in more detail in the following.

TABLE I

Evidence of Hepatocellular and Cholangiolar Functional Derangement Due to Diffuse Liver Disease

1. Hepatocellular :

- Increased delayed reacting bilirubin
- Increased urobilinogen in urine
- Diminished galactose clearance
- Diminished hippuric acid synthesis
- Diminished serum albumin
- Diminished cholesterol ester fraction
- Positive Hanger test (cephalin-cholesterol flocculation)
- Positive Maclagen test (thymol turbidity)? (vide infra)

2. Cholangiolar :

- Increased prompt reacting (1') bilirubin
- Bilirubinuria
- Bile salts in blood and urine
- Increased total cholesterol in blood
- Increased serum alkaline phosphatase

Patients with hepatitis are seen in whom the evidence of liver functional derangement is mainly hepatocellular and again, mainly cholangiolar. In many cases, various mixtures of the two are observed. The results of the present study, as well as of others conducted in recent years,<sup>2</sup> indicate that these variations are largely a matter of stage of the disease and that it is not possible to separate an hepatocellular form as a disease entity distinct from a cholangiolitic form, as has been suggested by Eppinger<sup>5</sup> and others.<sup>8</sup> It is nevertheless evident that the late stage of the disease is in some cases of a relatively pure cholangiolitic type, characterized mainly in other words by the evidences of cholangiolar functional disturbance. Closely correlated with these, especially the last three listed in table 1 is the presence of pruritus. Such cases, particularly if sporadic, offer real difficulty in diagnosis since they closely simulate extrahepatic biliary obstruction.

In studying liver function under any circumstances, and especially in a disease such as hepatitis in which serial observations, often on a large scale, are essential, it is clear that simple tests related to natural substances are preferable to more complex procedures especially those demanding administration of a given material and subsequent quantitative determination in blood or urine. This assumes, of course, that the simple procedures are of equal or greater value than the more complex ones which is not always the case, particularly if the stage of the disease be taken into account. Thus, the experience gained in the last two years, as exemplified in the report of Gellis and Stokes',<sup>9</sup> indicates that the simple procedure for bilirubin in the urine is probably fully as useful as the bromsulfalein test in the early stage of the disease. In the late defervescent period, on the contrary, the value of the two tests is quite reversed. This will be referred to again. The tests for bilirubin and urobilinogen in the urine are the only procedures which lend themselves readily to everyday bedside diagnosis. It was quite unfortunate, therefore, that when epidemic jaundice began to be a major

problem some five years ago, the great usefulness of these simple tests was often ignored or overlooked.

This may be ascribed to two causes: The neglect of the urine bilirubin test may be attributed to the generally accepted concept<sup>5, 10</sup> that bilirubin does not appear in the urine until the serum bilirubin has become elevated to 2 mg. per 100 c.c., a level in other words at which jaundice is usually manifest. As will be pointed out in more detail a little later, this concept has had to be abandoned. The cause of the rather general failure to utilize the Ehrlich reaction for urobilinogen in the urine appears to have been the relative insensitivity and frequently misleading results of the dilution technic of estimation such as that described by Wallace and Diamond.<sup>11</sup> This method, to be interpreted as positive, requires a color reaction with a dilution of 1:20, a dilution which excludes many instances in which there is a significant increase in urobilinogen excretion, especially if the urine be relatively dilute to begin with.

In discussing our experience with individual procedures used in the study of hepatitis, the serum and urine bilirubin will be considered first.

Neefe and his associates,<sup>7</sup> while studying infectious hepatitis which had been induced in human volunteers, observed that bilirubin often appeared in the urine at the onset of the disease *before* the total serum bilirubin had exceeded 1 mg. As already noted, this was contrary to general belief but it does appear that George Budd had recognized the same phenomenon as early as 1846.<sup>12</sup>

"The coloring matter of bile may be detected in the urine even before the skin becomes yellow and in some cases the readiness with which it passes off in the urine seems to prevent the occurrence of jaundice—the skin retaining its natural color while the tint of the urine attests to the presence of bile."

Although Budd did not estimate the serum bilirubin level, it seems highly probable that he was the first to describe hepatitis without jaundice, as well as the bilirubinuria in the preicteric stage of hepatitis with jaundice. In retrospect, it is really not too astonishing to find a lack of correlation of the presence or absence of bilirubinuria with the level of total serum bilirubin. It has long been known that in pure retention jaundice, as for example, hemolytic jaundice, in which the van den Bergh reaction is delayed or indirect, the total serum bilirubin may be considerably higher than 2 mg. and yet bilirubin is not found in the urine. Using the qualitative method only, van den Bergh<sup>13</sup> recognized long ago that the prompt reaction, which is associated with bilirubinuria, is usually complete within one minute, the delayed reaction taking place thereafter. This is better appreciated if one simply plots a direct van den Bergh reaction against time (figure 2), the prompt component being represented by a steep rise within the first minute, after which there is a rather abrupt shoulder and a slow continuous increase over a longer period.<sup>14, 15, 16</sup> If one adds alcohol at any point along this

latter part of the curve, one simply induces the remainder of the bilirubin to combine much more quickly with the diazo compound, bringing out what is known as the indirect reaction. If this had been done at 8 minutes, for example, the curve would have risen sharply again at that time. The delayed and indirect reacting bilirubins are believed to be identical. The available evidence suggests that this type is still attached to the globin derived from the hemoglobin molecule, while the prompt reacting type is probably sodium bilirubinate as formed in the bile.<sup>17</sup> Some investigators have believed that there is but one type of bilirubin, the difference between prompt and delayed reactions depending simply on time and amount. If this were true, however,

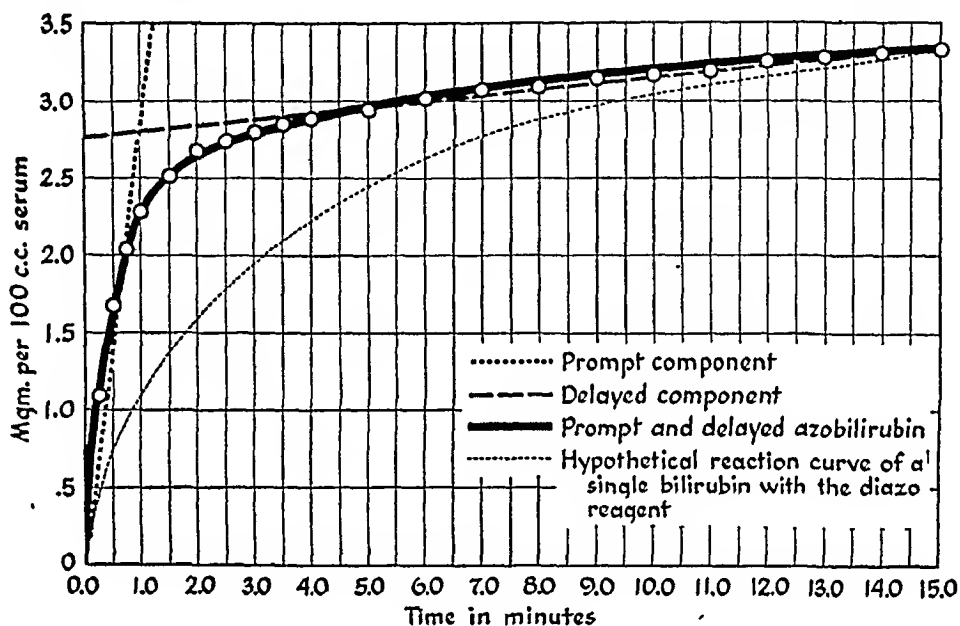


FIG. 2. Reaction curve of prompt and delayed direct reacting serum bilirubin compared with hypothetical (parabolic) curve of a single bilirubin with diazo reagent: (From article by C. J. Watson: Some newer concepts of the natural derivatives of hemoglobin, *Blood, Jr. of Hemat.*, 1946, i, 99.) Reproduced by permission of the publishers, Grune and Stratton, Inc., New York, N. Y.

one would expect a parabolic reaction curve, such as shown by the dotted line (figure 2) rather than that actually found, and which clearly reveals the presence of two distinct types.

There is much reason to believe that the prompt or one minute bilirubin, as represented by the more vertical component, is that which is related to the appearance of bilirubin in the urine.

Using the fundamental classification of jaundice as proposed by Rich,<sup>18</sup> regurgitation jaundice is characterized by an increase of prompt reacting bilirubin in the serum, together with bilirubinuria. In retention jaundice the delayed reacting bilirubin is increased and bilirubin is absent in the urine. The existing evidence indicates that regurgitation may occur because of increased intrabiliary pressure, with rupture of cholangioles, or toxic chol-

angiolar injury with increased permeability.<sup>5, 6</sup> This has been discussed in more detail in a recent communication.<sup>16</sup> As already noted, there is considerable reason to believe that the ampullae of the bile capillaries are most vulnerable in this regard, but the question must remain open for the time being as to whether there is regurgitation from the bile capillaries or whether the bilirubinglobin of the blood is converted to the prompt reacting bilirubin by the Kupffer cells and passed at once into the lymph, thence into the thoracic duct and thus into the blood. Recent studies by Gonzalez-Oddone,<sup>21</sup> in this laboratory, on experimental regurgitation jaundice in dogs, have shown that the prompt reacting bilirubin, along with other elements of the bile, gains access to the blood, at least in considerable measure, via the lymph. In these experiments, the bilirubin appearing in the thoracic duct lymph was almost wholly of the one minute or prompt reacting type.

Surprisingly enough, the range of values for the one minute or prompt reacting bilirubin in normal individuals has not been determined until recently.<sup>16</sup> Our experience thus far, at least, indicates that this does not exceed 0.2 mg. per 100 c.c., the great majority of values being less than 0.1. It is believed that the 1' and the total are the only values of importance, the difference, or T-1' representing the delayed or indirect type.

The study of cases of infectious hepatitis has shown that bilirubinuria may be present at the outset of the disease when but minor elevation of the prompt reacting bilirubin has occurred. A striking example was described in a previous report.<sup>16</sup>

The finding of bilirubin in the pre-icteric stage of hepatitis is quite in accord with the history that these patients commonly give of "dark urine for several days before the appearance of jaundice."

In the defervescent stage of the disease, however, bilirubin disappears from the urine at relatively high levels of the prompt reacting bilirubin, usually between 0.8 to 1.2, at times even higher.<sup>16</sup> In one case which we have studied, there was no bilirubinuria even though the prompt reacting serum bilirubin was 3.0 mg. It is evident that the renal threshold in the early or pre-icteric stage, is lower than it is during defervescence.

The importance of early bilirubinuria in diagnosis, especially in the pre-icteric stage of hepatitis, clearly indicated the need of a simple and reliable method which could be applied to mass and serial usage.

At the suggestion of Dr. Roy H. Turner, the "barium or filter strip" modification of Harrison's test for bilirubin in the urine was devised.<sup>23, 24</sup> It consists simply in impregnating strips of a specially retentive thick filter paper with barium chloride. These strips are then inserted into the urine sample to be tested, held perpendicularly for a moment or two during which the urine runs up by capillary attraction and the pigments collect at the surface of the urine. Fouchet's reagent is then dropped upon this surface zone with the result that if bilirubin is present, a green color is noted. The test is sensitive to as little as .05 mg. per 100 c.c. of urine, although in many

samples concentrations less than 0.1 mg. per 100 c.c. are doubtful. The method has been adapted to a semiquantitative colorimetric procedure.<sup>24</sup> The ease of application is obvious and it is believed that this test could be added with much advantage to the routine urinalysis. It may be regarded as one of the two tests of liver function which lend themselves to bedside diagnosis. The other is the urine Ehrlich reaction for urobilinogen.

It might be pertinent at this time to review very briefly the present concept of the origin and fate of urobilinogen (figure 3). As already noted, it

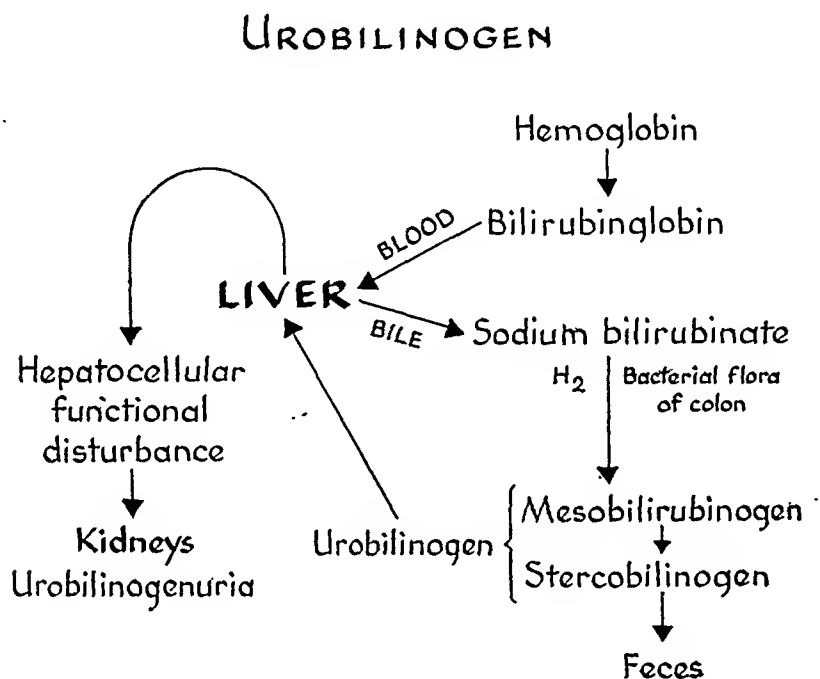


FIG. 3.

is believed that bilirubinglobin is changed in the liver to sodium bilirubinate and from this the urobilinogen is formed by the reducing action of the bacterial flora of the colon. Actually, two very similar colorless chromogens result, both of which fortunately give an Ehrlich reaction of equal intensity.<sup>25, 26</sup> The term "urobilinogen" refers to the composite of these two chromogens. As indicated in figure 3, a considerable fraction of the urobilinogen thus formed is reabsorbed from the colon into the portal circulation and returns to the liver, through which, if there is hepatocellular functional disturbance of any appreciable degree, the urobilinogen goes into the general circulation and is excreted by the kidneys. There are several "if's" in this sequence that must be taken into account in clinical diagnosis. Thus, if little or no bile reaches the intestine, urobilinogen will be found in a very small amount, or not at all, and even though the liver is injured, urobilinogen may not be found in the urine.<sup>27</sup> This state of affairs characterizes many cases of hepatitis during the most severe phase of the disease, when jaundice is at its peak and little or no bile is entering the intestine. If the intestinal



contents move through the colon so rapidly that there is little time for reduction or reabsorption, as for example, with marked diarrhea, there may not be urobilinogenuria even though liver damage exists. If there is enough renal insufficiency to cause nitrogen retention, urobilinogen may also be retained.<sup>28, 29</sup>

The qualitative Ehrlich reaction or test for urobilinogen in the urine is very simple.<sup>29</sup> It is particularly useful when applied serially by the same individual. It is recorded simply as a trace, indicated by a faint pink, on up to 4 plus, which is an intense red-blue color. The use of sodium acetate, as first recommended by Terwen,<sup>30</sup> is very important in this reaction.<sup>31</sup> In the first place it greatly intensifies the color, and in the second it largely or completely abolishes any color due to indole or skatole, which also react with the aldehyde.

In our experience, 95 per cent of normal individuals excrete less than one Ehrlich unit per 2 hour sample, while about 5 per cent excrete between 1 and 1.5 units.<sup>32a</sup> There is little doubt that the method is much more reliable if used serially, as the excretion of urobilinogen fluctuates from day to day and at various times within the same day. For this reason it must be emphasized that in some cases of liver disease the single or 2 hour sample may be normal, yet the 24 hour urine urobilinogen<sup>31</sup> may be considerably increased.<sup>32b</sup> Unfortunately, the latter determination does not lend itself well to mass or serial usage.

Hallock and Head<sup>33</sup> have used the semi-quantitative urine Ehrlich method in studying a group of cases of hepatitis seen during the first few days of the disease. Twenty of these subsequently developed jaundice, of which number 18 exhibited significantly positive Ehrlich reactions during the pre-icteric stage. They also studied 78 individuals in the same epidemic who did not develop jaundice subsequently, and who were classified as cases of hepatitis without jaundice although it was known \* that quite a number of this group had dark urine and slightly elevated icterus indices. In this group 88 per cent had positive reactions, as compared with 5 per cent in the control series.

Table 2 includes the data from one of Hallock and Head's cases showing the early appearance of urobilinogen with a normal icterus index, the fluctuation in amount from day to day, the disappearance at the height of the jaundice, and then the return during the early defervescent stage. It may be emphasized that this return of urobilinogen in the urine, in other words, the change from a negative to a positive Ehrlich reaction, often heralds beginning improvement. It may be noted that they compared the simple qualitative and the semiquantitative methods, their results indicating that in the hands of the same individual the former method is very helpful. Table 3 includes data from one of Hallock and Head's cases of hepatitis without jaundice. This shows the outspoken urobilinogenuria at the outset of the disease and the rapid disappearance as the patient improved. Our own experience with

\* Personal communication.

TABLE II\*

Urine Ehrlich Reaction in Epidemic Hepatitis, Pre-Icteric and Icteric Stages

	4 p.m.		9 p.m.		Ceph. Floc. Reaction 24 hr.	I.I.	Hepatic	
	Qual.	Quant. Ehrlich Units/100 c.c.**	Qual.	Quant. Ehrlich Units/100 c.c.**			En.	Tend.
Nov. 22	3+	3.2	0		0	6	1	++
Nov. 23	Trace	0.6	Trace	0.6				
Nov. 24	1+	1.2	0					
Nov. 25	2+	2.4	2+	2.4			1	++
Nov. 26	4+	4.0	4+	4.8				
Nov. 29	4+	8.6	0		3+	33		
Dec. 1	2+	2.4	1+	1.2				
Dec. 3	Trace	0.6	0		3+			
Dec. 5	0		0			74	1	++
Dec. 6	0		0					
Dec. 7	1+	1.2	0				1	++
Dec. 9	2+	2.0					1	++
Dec. 11	4+	8.0			2+	36	1	++
Dec. 13	4+	8.0						
Dec. 18	4+	5.0						
Dec. 23	1+	1.6			1+	16		
Dec. 26	0	0					0	0
Dec. 29	0	0					0	0

I.I.—Icteric index.

En.—Hepatic enlargement in terms of fingers'-breadth below costal margin.

Tend.—Hepatic tenderness in terms of 1 to 3 plus.

\* From the Bulletin of the U. S. Army Medical Department, 1946, v, 240. Reproduced by permission of the Surgeon General, War Department, Washington, D. C.

\*\* In the original this was given, incorrectly, as mg. of urobilinogen per 100 c.c.

TABLE III\*

Urine Ehrlich Reaction in a Case of Epidemic Hepatitis without Jaundice

	4 p.m.		9 p.m.		Ceph. Floc. Reaction 24 hr.	I.I.	Hepatic	
	Qual.	Quant. Ehrlich Units/100 c.c.**	Qual.	Quant. Ehrlich Units/100 c.c.**			En.	Tend.
Nov. 16	4+	6.0	2+	2.4	0	9	1	++
Nov. 17	3+	4.0	1+	1.6			1	++
Nov. 18	3+	4.0	1+	1.6	0		1	++
Nov. 19	Trace	0.60	0				1	++
Nov. 20	Heavy Trace	0.80	0		0			
Nov. 21	0		0			11	1	++
Nov. 22	0		0		0			
Nov. 23	0		0				0	+
Nov. 24	0		0			8	0	0
Nov. 25	0		0		0			
Nov. 26	0		0					
Nov. 27	0		0			9	0	0

Key of abbreviations as given under table 2.

\* From the Bulletin of the U. S. Army Medical Department, 1946, v, 239. Reproduced by permission of the Surgeon General, War Department, Washington, D. C.

\*\* In the original this was given incorrectly, as mg. of urobilinogen per 100 c.c. .

the urine Ehrlich reaction in hepatitis indicates that the patient should not be allowed to resume activity until it has returned to and remained at a normal level for several days. Other factors, including of course laboratory data such as is discussed below, must also be taken into account in determining when it is reasonably safe for resumption of activity. As noted at the outset it is believed that any one test of liver function should not be relied upon too strongly, and that composite studies or "profiles" of liver function are more likely to reveal the truth about the presence or absence of liver injury or disease, and at the same time to give some insight into its type and extent. In previous reports<sup>23, 4a, 4b</sup> we have described the use of a single chart to depict a composite study, or "profile" of liver function. While this has proved very helpful and instructive, we have sought to improve the method, and for some time now, have been studying the usefulness of three liver function schedules to facilitate the recording of composite studies. These are printed on small squares of gummed paper which may then be attached to sheets of chart size for incorporation in the patient's record. These schedules have proved very helpful, not only in screening patients for evidence of liver disease, but also in differential diagnosis, and in following the progress of the disease in any given case. The profiles obtained by charting the data in this way, are often indicative of a certain type of jaundice or liver disease.

Schedule No. 1 (figure 4) is used in non-jaundiced cases. It includes, from left to right, the 1 minute or prompt reacting serum bilirubin, and the delayed or total minus 1 minute fraction; this permits ready comparison of the degree of retention and regurgitation factors. The thymol turbidity, indicated by T units, is in the next column; this is a procedure described recently by Maclagan<sup>34</sup> which is probably based on an increase of a certain type of globulin or globulin-lipid complex.<sup>35</sup> The cephalin cholesterol flocculation test (C.C.) of Hanger is included at the top of this column, the result being inserted in terms of a trace to 4+. Schedule No. 1 also includes the bromsulfalein retention in per cent, 45 minutes after the administration of 5 mg. of dye per kilogram of body weight. As noted there are two columns for the urine Ehrlich reaction in units, on successive days, and one for the urine urobilinogen in mg. for a 24 hour period. The latter, however, need not be done if one or both of the urine Ehrlich tests are significantly elevated. The last column is for the urine coproporphyrin in  $\gamma$  per 24 hours. Lack of this determination need not exclude use of the schedule, although, as noted subsequently, it may often provide valuable information. The "barium strip" modification of the Harrison test for bilirubinuria, as indicated by H, is recorded with the prompt reacting bilirubin, with which, as we have already seen, it is correlated. The horizontal line between the N's represents the upper limit of normal. Values above this line are indicative of liver functional impairment, although it should be emphasized that such elevations, especially when considered singly, may

relate to diseases other than those originating intrinsically in the liver. For example one might find a slight but distinct elevation of the prompt reacting serum bilirubin in a case of common duct calculus without visible jaundice, or one might see a similar elevation of the delayed reacting bilirubin in such conditions as pernicious anemia, hemolytic anemia, or constitutional hepatic dysfunction.

## Liver Function Schedule No. 1

Name ..... Hospital No. ....

Dates .....

H=		CC=					
2.0	2.6			10	10		
1.8	2.4			9	9		400
1.6	2.2			8	8	10	350
1.4	2.0	16	35	7	7	9	300
1.2	1.8	14	30	6	6	8	250
1.0	1.6	12	25	5	5	7	200
0.8	1.4	10	20	4	4	6	175
0.6	1.2	8	15	3	3	5	150
0.4	1.0	6	10	2	2	4	125
N	0.2	4	5	1	1	3	100
	0.0	2	0	0	0	2	75
				2 days		1	50
						0	25
S. B. 1'	S. B. T-1'	T. Units	B. 5 mg. per kilo. % at 45'	U. E. Units per 2 hr. spec.	U. U. mg. per 24 hr.	U. C. P. γ per 24 hr.	
Mq. per 100 cc. serum							

FIG. 4.

- S. B. 1' = One minute or prompt reacting serum bilirubin.  
 S. B. T-1' = Delayed direct and indirect reacting serum bilirubin (T = total).  
 H. = Bilirubin in urine (barium strip modification of Harrison's test).  
 CC = Cephalin-cholesterol flocculation test (24 hour reading).  
 T = Thymol turbidity test (30' reading).  
 B = Bromsulfalein retention 45' after 5 mg. per kilo. body wt.  
 U. E. = Urobilinogen in urine (Ehrlich units).  
 U. U. = Urobilinogen in urine (milligrams).  
 U. C. P. = Coproporphyrin in urine (gamma).

Liver function Schedule 2 (figure 5) is of particular utility for the jaundiced patient. This schedule is used in differential diagnosis of jaundice and in following the jaundiced patient with respect to progress of the disease. It may also be employed to render the study of any obscure case more complete. It differs from Schedule No. 1 in omitting the bromsulfalein, experience having shown that this test has little or no practical value in the presence of appreciable jaundice. In addition, Schedule No. 2 includes the feces Ehrlich determination which gives an insight into the degree of biliary

obstruction or exclusion of bile from the intestine. This is, however, unnecessary if the urine Ehrlich reaction is significantly increased.

It is seen that a column for the 24 hour urine urobilinogen has been omitted. This determination is regularly carried out, however, in those instances in which the two urine Ehrlich values are negative or border line, and where the diagnosis is still in doubt. In some instances, too, the simple

Liver Function Schedule No.2

Name .....				Hospital No. ....						
Dates .....										
20.0	20.0									
18.0	18.0									
16.0	16.0									
14.0	14.0	0								
12.0	12.0	1								
10.0	10.0	2								
8.0	8.0	3	10	10						
6.0	6.0	4	9	9						
4.0	4.0	5	8	8		25				
2.0	2.0	10	7	7	16	50	0			
1.5	1.8	20	6	6	14	75	20			
1.0	1.6	30	5	5	12	100	45			
0.8	1.4	40	4	4	10	125	65			
0.6	1.2	50	3	3	8	150	85			
0.4	1.0	75	2	2	6	175	105			
N	0.2	0.8	100	1	1	4	200	125	4	N
				0	0	2	250	150	8	
				2 days			300	175	12	
							400	200	20	
							500		30	
									40	
	S.B. 1'	S.B. T-1'	F.E. Units per 100Gm.	U.E. Units per 2 hr. spec.	T Units	C Mg. per 100 cc. serum	C.E. Mg. per 100 cc. serum	P. Alk.		

FIG. 5.

- S. B. 1' = One minute or prompt reacting serum bilirubin.  
 S. B. T-1' = Delayed direct and indirect reacting serum bilirubin (T = total).  
 F. E. = Urobilinogen in feces (Ehrlich units).  
 U. E. = Urobilinogen in urine (Ehrlich units).  
 CC = Cephalin-cholesterol flocculation test (24 hour reading).  
 T = Thymol turbidity test (30' reading).  
 C = Total serum cholesterol.  
 C. E. = Cholesterol ester content of serum.  
 P = Phosphatase, alkaline, in Bodansky units per 100 c.c. serum.

quantitative Ehrlich reaction is interfered with by the large amounts of bilirubin present in the urine, and in these it is best to determine the 24 hour urine urobilinogen value.<sup>32b</sup>

The total urinary coproporphyrin determination has also been omitted as experience has shown that it is of little differential diagnostic value in the presence of regurgitation jaundice, whether due to liver injury or extra-hepatic biliary obstruction. This study will be discussed in detail elsewhere.

Schedule No. 2 further includes the cholesterol and cholesterol esters and the alkaline phosphatase determination. The total cholesterol is elevated in many cases of obstructive jaundice and in certain cases of paren-

chymal jaundice although it is usually normal or reduced in severe hepatic disease. Since a reduction is more likely to indicate diminishing hepatocellular function, the direction of increase has been placed below the line and the decrease above. The cholesterol esters are characteristically diminished when there is hepatocellular functional derangement. This method has value, however, only if a reliable procedure for determination of cholesterol esters is used, such as the Sperry-Schoenheimer technic.<sup>36</sup> Furthermore, it may be emphasized that the percentage of esterified cholesterol may diminish markedly in the presence of high grade, extra-hepatic biliary obstruction of long standing, hence the value of this finding in differential diagnosis is limited. Marked elevation of alkaline phosphatase occurs when cholangiolar function is disturbed and hepatocellular function is relatively normal, as for example, in the cholangiolitic type of hepatitis and cirrhosis, examples of which will be mentioned. With diminishing hepatocellular function, as in the more severe liver injuries, the alkaline phosphatase is commonly normal or not more than slightly increased. Gutman and his co-workers<sup>37</sup> found that in parenchymal jaundice the alkaline phosphatase is usually less than 10 Bodansky units, while in jaundice due to extrahepatic biliary obstruction it is

## Liver Function Schedule No.3

Name.....				Hospital No. ....			
Dates.....							
			1 hr. PSP .....%			..... hrs after ..... mg. of vitamin K	
			0	32		32	
			.1	28		28	
1.5			.2	24		24	
2.0	4.5		.3	20	20	20	20
2.5	4.0		.4	18	18	18	18
3.0	3.5		.5	16	16	16	16
3.5	3.0		.6	14	14	14	14
N	4.0	2.5	.7	12	12	12	12
S.A.	S.G.	H.A.	P.T.	P.T.R.			
Gm. per 100 cc.	Gm. per	Gm. per	Patient Control	Patient Control			
serum	cc.	hr.	Time in seconds				

FIG. 6.

S. A. = Serum albumin.

S. G. = Serum globulin.

H. A. = Hippuric acid in urine, one hour after intravenous injection of 1.77 gm. of sodium benzoate (p.s.p. test performed simultaneously).

P. T. = Prothrombin time (Quick's method).

P. T. R. = Prothrombin time response (after vitamin K therapy).

usually well above this level. Because of this we have made the direction of diminution upward in Schedule No. 2, with 4.0 Bodansky units as the upper limit of normal.

Liver function Schedule No. 3 (figure 6) is a supplementary schedule which, so far as the hepatitis problem is concerned, need be used only in exceptional instances. This schedule is of value for differential diagnosis in obscure cases, especially in the presence of ascites, and also in following the progress of the disease in certain instances. It will be noted that the schedule includes, in addition to the fractional serum proteins, the intravenous hippuric acid test, the prothrombin time, and the prothrombin response to vitamin K in those instances in which the initial prothrombin time is abnormal.

Some specific examples of the variations of liver function in hepatitis may now be presented and discussed. Seven cases have been selected because of various points which they emphasize.

The first case is one of epidemic hepatitis in a boy of 14 (L. T.) without jaundice but with dark urine for several days at the outset of the illness, the early period being further characterized by anorexia, nausea and vomiting. The liver was easily palpable and tender. The mother and two brothers also had the disease, the mother being jaundiced. The first composite liver function study is shown in figure 7a. As noted the serum bilirubin, espe-

Liver Function Schedule No. 1						
Name <u>L. T.</u>			Hospital No. <u>753592</u>			
Dates <u>4-10-45</u> to <u>4-11-45</u>						
H=+		CC=3+				
2.0	2.6			10	10	
1.8	2.4			9	9	400
1.6	2.2			8	8	350
1.4	2.0	16	35	7	7	300
1.2	1.8	14	30	6	6	250
1.0	1.6	12	25	5	5	200
0.8	1.4	10	20	4	4	175
0.6	1.2	8	15	3	3	150
0.4	1.0	6	10	2	2	125
0.2	0.8	4	5	1	1	100
0.0	0.4	2	0	0	0	75
				2 days	1	50
					0	25
S.B. 1'	S.B. T-1'	T. Units	B. 5 mg. per kilo % at 45'	U.E. Units per 2 hr. spec.	U.U. mg. per 24 hr.	U.C.P. γ per 24 hr.
Mg. per 100 cc. serum						

FIG. 7a. Case 1. Laboratory studies at time of admission.

cially the prompt reacting component, was distinctly elevated in spite of the lack of visible jaundice. The barium strip test revealed bilirubin in the urine. The other evidences of hepatic functional derangement are shown. A variation in the urine Ehrlich reaction from day to day may be seen. The patient recovered quickly and a week later the liver function study revealed marked improvement, the only residual abnormality being a slightly positive Hanger test and thymol turbidity (figure 7b).

## Liver Function Schedule No. 1

Name L.T. Hospital No 753592Dates 4-18-45

H <sub>2</sub> O		CC=2+					
2.0	2.6			10	10		
1.8	2.4			9	9		400
1.6	2.2			8	8	10	350
1.4	2.0	16	35	7	7	9	300
1.2	1.8	14	30	6	6	8	250
1.0	1.6	12	25	5	5	7	200
0.8	1.4	10	20	4	4	6	175
0.6	1.2	8	15	3	3	5	150
0.4	1.0	6	10	2	2	4	125
N	0.2	4	5	1	1	3	100
	0.0	2	0	0	0	2	75
				2 days		1	50
						0	25
S.B.	S.B.	T.	B.	U.E.	U.U.	U.C.P.	
1'	T-1'	Units	5 mg.	Units	mg.	γ	
Mg. per 100 cc.			per kilo	per	per	per	
serum			% at	2 hr.	24 hr.	24 hr.	
			45'	spec.			

FIG. 7b. Case 1. Laboratory studies after one week's hospitalization.

Figure 8a shows the liver function profile from a brother of the preceding case (Case 2, D.T. ♂, 16). This individual had the same sort of an attack at about the same time, also without jaundice but with the abnormal findings as shown. He appeared to recover but, contrary to advice, resumed activity, including the use of alcohol, too soon, and developed a severe relapse, this time with outspoken jaundice, together with marked evidence of hepatocellular functional derangement consisting of high urobilinogen in the urine, markedly positive thymol turbidity, slightly elevated total cholesterol, but low cholesterol esters and relatively low phosphatase (figure 8b). After a prolonged period of bed rest, this patient apparently recovered. A third (partial) composite study was carried out 10½ months later. This is shown in figure 8c.

The third case (K.W. ♂, 32) is that of a severe prolonged epidemic hepatitis with marked jaundice. The composite study in this instance



## Liver Function Schedule No. 1

Name D.T. Hospital No. 736684  
 Dates 4-10-45 to 4-11-45

H=0		CC=2+					
2.0	2.6			10	10		
1.8	2.4			9	9		400
1.6	2.2			8	8	10	350
1.4	2.0	16	35	7	7	9	300
1.2	1.8	14	30	6	6	8	250
1.0	1.6	12	25	5	5	7	200
0.8	1.4	10	20	4	4	6	175
0.6	1.2	8	15	3	3	5	150
0.4	1.0	6	10	2	2	4	125
0.2	0.8	4	5	1	1	3	100
0.0	0.4	2	0	0	0	2	75
				2 days		1	50
						0	25
S.B. I'	S.B. T-I'	T. Units	B. 5 mg. per kilo % at 45'	U.E. Units per 2 hr. spec.	U.U. mg. per 24 hr.	U.C.P. γ per 24 hr.	
Mg. per 100 cc. serum							

FIG. 8a. Case 2. Laboratory studies at time of first admission. Evidence of hepatitis without jaundice.

## Liver Function Schedule No. 2

Name D.T. Hospital No. 736684  
 Dates 6-26-45

20.0	20.0			CC=3+		%=19	
18.0	18.0						
16.0	16.0						
14.0	14.0	0					
12.0	12.0	1					
10.0	10.0	2	10	10			
8.0	8.0	3	9	9			
6.0	6.0	4	8	8	25		
4.0	4.0	5	7	7	50	0	
2.0	2.0	10	6	6	14	75	20
1.5	1.8	20	5	5	12	100	45
1.0	1.6	30	4	4	10	125	65
0.8	1.4	40	3	3	8	150	85
0.6	1.2	50	2	2	6	175	105
0.4	1.0	75	1	1	4	200	125
0.2	0.8	100	0	0	2	250	150
			2 days			300	175
						400	200
						500	30
S.B. I'	S.B. T-I'	F.E. Units per 100 Gm.	U.E. Units per 2 hr. spec.	T Units	C Mg. per 100 cc. serum	C.E. per 24 hr.	P. Alk.
Mg. per 100 cc. serum							

FIG. 8b. Case 2. Laboratory studies at time of second admission with relapse.

## Liver Function Schedule No.1

Name D.T. Hospital No. 736 684  
 Dates 6-1-46

H <sub>2</sub> O	CC=O					
2.0	2.6			10	10	
1.8	2.4			9	9	400
1.6	2.2			8	8	350
1.4	2.0	16	35	7	7	300
1.2	1.8	14	30	6	6	250
1.0	1.6	12	25	5	5	200
0.8	1.4	10	20	4	4	175
0.6	1.2	8	15	3	3	150
0.4	1.0	6	10	2	2	125
N 0.2	0.8	4	5	1	1	100
0.0	0.4	2		0	0	75
				2 days		50
						25
S.B. 1'	S.B. T-1'	T. Units	B. 5 mg. per kilo % at 45'	U.E. Units per 2 hr. spec.	U.U. mg. per 24 hr.	U.C.P. γ per 24 hr.
Mg. per 100 cc. serum						

FIG. 8c. Case 2. Laboratory studies 10½ months after apparent recovery.

## Liver Function Schedule No.2

Name K.W. Hospital No. ....  
 Dates 5-3-45

20.0	20.0		20	CC=tr.		%=
18.0	18.0					
16.0	16.0					
14.0	14.0	0				
12.0	12.0	1				
10.0	10.0	2				
8.0	8.0	3	10	10		
6.0	6.0	4	9	9		
4.0	4.0	5	8	8	25	
2.0	2.0	10	7	7	50	0
1.5	1.8	20	6	6	14	75
1.0	1.6	30	5	5	12	100
0.8	1.4	40	4	4	10	125
0.6	1.2	50	3	3	8	150
0.4	1.0	75	2	2	6	175
N 0.2	0.8	100	1	1	4	200
			0	0	2	250
			2 days			300
		179				400
						500
S.B. 1'	S.B. T-1'	F.E. Units per 100 gm.	U.E. Units per 2 hr. spec.	T Units	C Mg. per 100 cc. serum	C.E. P. Alk.
Mg. per 100 cc. serum						

FIG. 9. Case 3. Laboratory studies in case of prolonged epidemic hepatitis.

illustrates a rather striking degree of dissociation in the evidence of liver injury (figure 9). The urine Ehrlich was very high, but the Hanger test and the thymol turbidity were consistently negative. The phosphatase was moderately increased. Unfortunately, the cholesterol esters were not determined. From a differential diagnostic standpoint, the urine Ehrlich was most helpful in this instance since the Hanger test and the phosphatase were both more suggestive of an extrahepatic biliary obstruction. A large amount of urobilinogen in the urine, together with a history of exposure, and a rather marked tenderness of the liver, permitted the correct diagnosis. The patient subsequently made a complete recovery.

The fourth case (E.S. ♀, 38) is another example of a dissociation of liver functional derangement. When first seen, this patient had marked jaundice and severe pruritus. As noted in the first composite study shown in figure 10a, there was no urobilinogen in the urine at this time, and the patient

Liver Function Schedule No.2									
Name <b>E. S.</b>				Hospital No. <b>75 X 245</b>					
Dates <b>10-6-45</b>									
20.0	20.0								
18.0	18.0								
16.0	16.0								
14.0	14.0	0							
12.0	12.0	1							
10.0	10.0	2							
8.0	8.0	3	10	10					
6.0	6.0	4	9	9					
4.0	4.0	5	8	8					
2.0	2.0	10	7	7	16	25			
1.5	1.8	20	6	6	14	50	0		
1.0	1.6	30	5	5	12	75	20		
0.8	1.4	40	4	4	10	100	45		
0.6	1.2	50	3	3	8	125	65		
0.4	1.0	75	2	2	6	150	85		
N						175	105		
0.2	0.8	100	1	1	4	200	125	4	N
			0	0	2	250	150	8	
			2 days			300	175	12	
						400	200	20	
						500		30	
S.B.	S.B.	F.E.	U.E.	T		C	C.E.		
1'	T-1'	Units	Units	Units		Mg. per 100 cc.			
Mg. per 100 cc. serum		per 100 Gm.	per 2 hr. spec.			serum			
							P.		
							Alk.		

FIG. 10a. Case 4. Laboratory studies at time of admission. In figures 10a and 10b the values for the alkaline phosphatase are expressed in King-Armstrong units. (The Bodansky method could not be used at this time due to unavailability of Elon.)

probably had a rather complete exclusion of bile from the intestine, although this was not proved by means of the feces Ehrlich determination, which ought to have been done but was omitted. The high total cholesterol and the very high phosphatase were more suggestive of an extrahepatic biliary obstruction, but the finding that the cholesterol esters were only 27 per cent pointed somewhat more toward a diffuse hepatocellular functional disturbance. In other words, while the total cholesterol and the phosphatase

tase values indicated cholangiolar regurgitation of bile and would have failed to differentiate between extrahepatic obstructive jaundice and cholangiolitic hepatitis, the low percentage of cholesterol esters supported the latter diagnosis, since this finding pointed clearly to a concomitant, diffuse hepatocellular injury. The composite study of the second period, as shown in figure 10b, reveals a lessening intensity of jaundice, the presence of increased uro-

Liver Function Schedule No.2

Name E.S. Hospital No. 758245

Dates 10-11-45

20.0 18.0 16.0 14.0 12.0 10.0 8.0 6.0 4.0 2.0 1.5 1.0 0.8 0.6 0.4 0.2		20.0 18.0 16.0 14.0 12.0 10.0 8.0 6.0 4.0 2.0 1.8 1.6 1.4 1.2 1.0 0.8				C.C.=		% = 20	
		0		10	10				
		1		9	9				
		2		8	8				
		3		7	7				
		4		6	6	16	25	0	
		5		5	5	14	75	20	
		10		4	4	12	100	45	
		20		3	3	10	125	65	
		30		2	2	8	150	85	
		40		1	1	6	175	105	
		50		0	0	4	200	125	
		75		0	0	2	250	150	
		100		0	0		300	175	
				2 days			400	200	
							500		
S.B. 1'	S.B. T-1'	F.E. Units per 100Gm.	U.E. Units per 2 hr. spec.	T Units	C Mg. per 100 cc. serum	C.E. P. Alk.			

FIG. 10b. Case 4.

bilinogen in the urine indicating a resumption of bile flow into the intestine. The lack of qualitative abnormality of the serum proteins is evidenced by the negative Hanger test and normal thymol turbidity. It may be noted that if one had employed only the cephalin flocculation, the total cholesterol and the alkaline phosphatase determinations, one would unquestionably have been misled in the direction of a simple obstructive jaundice and an unnecessary and even hazardous surgical procedure. This emphasizes again the value of a composite study. As has been noted, the patient complained bitterly of pruritus, and was literally covered with excoriations. The blood bile acid determination by Josephson's method<sup>38</sup> revealed an elevation to 4.0 mg. per 100 c.c., or about eight times the normal. This is mentioned only because there is much reason to believe that the bile acid level in the blood is correlated in some way with the degree of pruritus in cases of jaundice. In our experience, the bile acids, total cholesterol and alkaline phosphatase are usually elevated in rather similar fashion, and there is reason to believe that this elevation is a direct manifestation of regurgitation of bile

into the blood; in other words, of regurgitation jaundice. Another question that deserves consideration in this regard, is whether in such instances there may perhaps be an actual over production of phosphatase in the liver, possibly even in the cholangiolar epithelium. We consider this possibility simply because the values that are seen in these instances are often so high that one is led to doubt that all of the increase is due simply to regurgitation of a normal, or relatively normal bile.

The liver biopsy in case 4 revealed evidence of but a mild, although quite definite cholangiolitic hepatitis. The portal spaces contained a con-

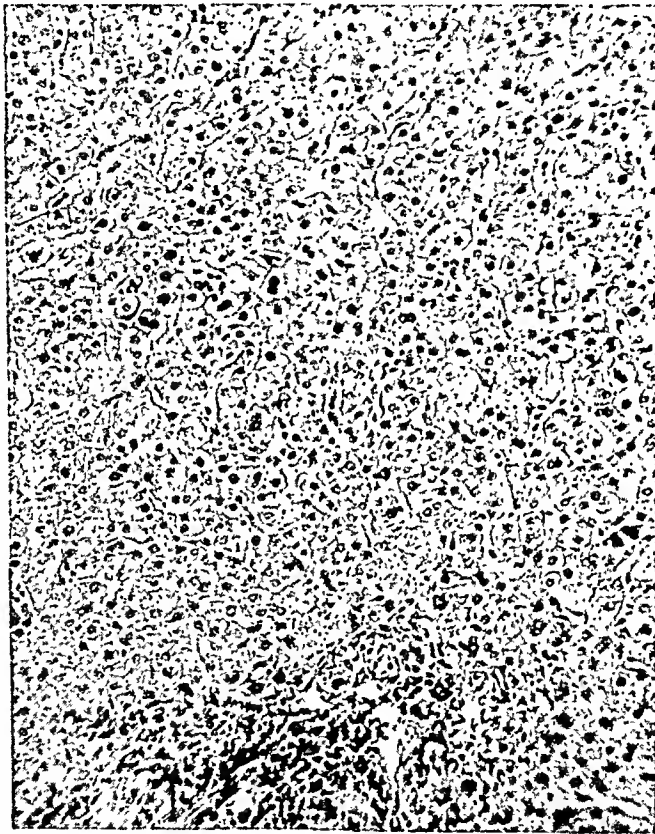


FIG. 10c. *Case 4.* Photomicrograph  $\times 175$ . Stained microscopic section of liver biopsy secured October 30, 1945 at time of peritoneoscopy. (See text.)

siderable number of mononuclear leukocytes and a small number of neutrophils (figure 10c). Occasional necrotic liver cells surrounded by leukocytes, were observed. A few bile thrombi were seen. The lack of evidence of obstruction in the intrahepatic biliary tract lends support, as it has in other instances, to the belief that the regurgitation of bile is due to a functional injury and increased permeability of the cholangiolar epithelium.

Case 5 (A.G. ♂, 21) is an example of a chronic active hepatitis with previous jaundice, in which a thorough examination of liver function by ordinary methods failed to reveal anything of significance, although there

could be little doubt even from the clinical standpoint that the patient was having continued activity of his disease. This case was that of a male of 21 years who suffered from a severe attack of (sporadic) hepatitis with jaundice between October 20 and January 1, 1945. In March, 1946 nearly three months after disappearance of jaundice, the liver was enlarged and tender, and the spleen was easily palpable. A biopsy of the liver at this time revealed definite evidence of an active hepatitis consisting of periportal lymphocytic infiltration, occasional abnormal liver cells, and some small areas of actual necrosis (figure 11a).

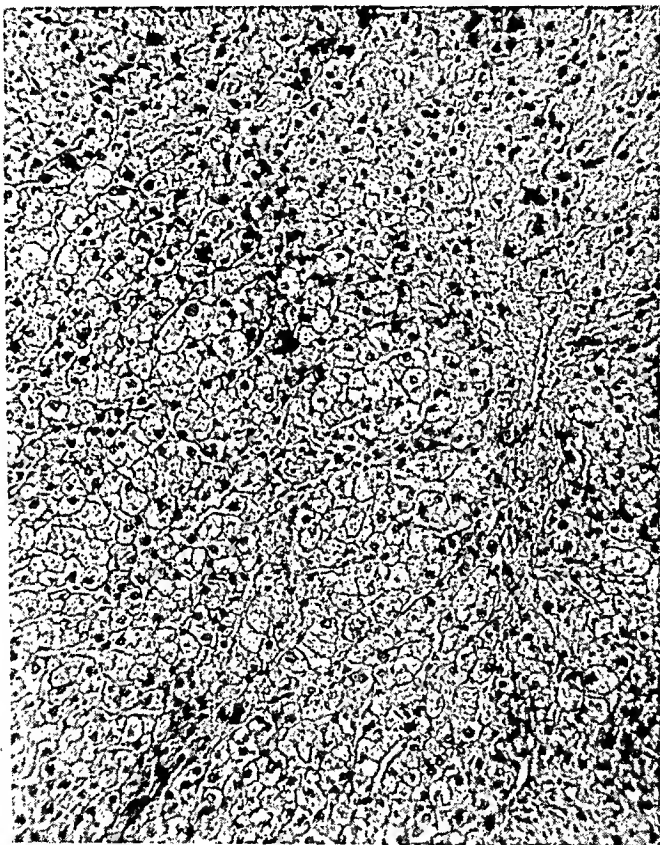


FIG. 11a. Case 5. Photomicrograph  $\times 175$ . Liver biopsy secured March 14, 1946 at time of peritoneoscopy.

In this case, surprisingly enough, the tests in all three liver function schedules were within normal limits (figures 11b, 11c and 11d), with exception of the 24 hour urine urobilinogen and coproporphyrin (figure 11b). This case represents one of the exceptions in which the serial urine Ehrlich reaction on single samples was normal, but the 24 hour urine urobilinogen was distinctly elevated. This means simply that one cannot place a blind reliance on single urine samples, or samples collected for a small fraction of the 24 hour period. While, as previously stated, it is usually true that abnormal amounts of urobilinogen, if any, are excreted in the late morning or

## Liver Function Schedule .No.1

Name A. G. Hospital No. 763650  
 Dates 3-7-46

H=0		CC=0				
2.0	2.6			10	10	
1.8	2.4			9	9	400
1.6	2.2			8	8	350
1.4	2.0	16	35	7	7	300
1.2	1.8	14	30	6	6	250
1.0	1.6	12	25	5	5	200
0.8	1.4	10	20	4	4	175
0.6	1.2	8	15	3	3	150
0.4	1.0	6	10	2	2	125
N	0.2	4	5	1	1	100
	0.0	0	0	0	0	75
	0.4			2 days	1	50
					0	25
S.B. I'	S.B. T-I'	T. Units	B. 5 mg. per kilo % at. 45'	U.E. Units per 2 hr. spec.	U.U. mg. per 24 hr.	U.C.P. γ per 24 hr.
Mg. per 100 cc. serum						

FIG. 11b. Case 5. Laboratory studies three months after disappearance of jaundice.

## Liver Function Schedule .No.2

Name A. G. Hospital No. 763650  
 Dates 3-8-46

20.0	20.0			CC=0		%=73
18.0	18.0					
16.0	16.0					
14.0	14.0	0				
12.0	12.0	1				
10.0	10.0	2				
8.0	8.0	3	10	10		
6.0	6.0	4	9	9		
4.0	4.0	5	8	8	25	
2.0	2.0	10	7	7	50	0
1.5	1.8	20	6	6	75	20
1.0	1.6	30	5	5	100	45
0.8	1.4	40	4	4	125	65
0.6	1.2	50	3	3	150	85
0.4	1.0	75	2	2	175	105
N	0.2	100	1	1	200	125
	0.8		0	0	250	150
			2 days		300	175
					400	200
					500	
S.B. I'	S.B. T-I'	F.E. Units per 100 Gm.	U.E. Units per 2 hr. spec.	T Units	C Mg. per 100 cc. serum	C.E. P. Alk.
Mg. per 100 cc. serum						

FIG. 11c. Case 5. Further analysis of liver function.

afternoon, it is evident from the present example that there are exceptions in which the excessive urobilinogen is excreted at other times during the 24 hours. This case also brings to attention a method of studying liver function to which we have not yet referred, namely, the excretion of coproporphyrin in the 24 hour urine. This will be discussed in detail in a separate communication,<sup>39</sup> and it will suffice to say here that it is a method which is proving of considerable value in the detection of latent liver damage, residual

## Liver Function Schedule No.3

Name A. G. Hospital No. 763650  
 Dates 3-19-46

		1 hr. PSP 5.8%		..... hrs after ..... mg. of vitamin K	
		0	32	32	
		.1	28	28	
1.5		.2	24	24	
2.0	4.5	.3	20	20	20
2.5	4.0	.4	18	18	18
3.0	3.5	.5	16	16	16
3.5	3.0	.6	14	14	14
N-4.0	2.5	.7	12	12	12
		1.5			
S.A.	S.G.	H.A.	P.T.	P.T.R.	
Gm. per 100 cc.		Gm. per	Patient Control	Patient Control	
serum		hr.	Time in seconds		

FIG. 11d. Case 5. Supplementary studies of liver function.

or chronic hepatitis, and early cirrhosis. There are other causes of elevation of the urine coproporphyrin, such as heavy metals, and chemical poisons, and in interpreting the results, one must, therefore, relate the findings to the history and to other features that may be present in any given case. The present case (figure 11b) is an example of the value of the procedure in late stage or chronic residual active hepatitis.

Case 6 (G.C.Z. ♂, 32) is an instance of chronic hepatitis of even longer duration, the patient having had his initial attack of jaundice over a year previously. Persistent bromsulfalein retention had been noted elsewhere. A biopsy was not done in this case, and the possibility of an early cirrhosis cannot be excluded, especially inasmuch as a number of spider nevi were observed on the skin. As noted in figure 12 the thymol turbidity, bromsulfalein, urine Ehrlich, and urine coproporphyrin were all elevated, somewhat over a year following the initial attack.



## Liver Function Schedule No. I

Name G. C. Z. Hospital No. O. P. D.Dates 4-4-46

H <sub>2</sub>		CC=0				
2.0	2.6			10	10	
1.8	2.4			9	9	400
1.6	2.2			8	8	350
1.4	2.0	16	35	7	7	300
1.2	1.8	14	30	6	6	250
1.0	1.6	12	25	5	5	200
0.8	1.4	10	20	4	4	175
0.6	1.2	8	15	3	3	150
0.4	1.0	6	10	2	2	125
N 0.2	0.8	4	5	1	1	100
0.0	0.4	2	0	0	0	75
				2 days		50
						25
S.B. 1'	S.B. T-1'	T. Units	B. 5 mg. per kilo % at 45'	U.E. Units per 2 hr. spec.	U.U. mg. per 24 hr.	U.C.P. γ per 24 hr.
Mg. per 100cc. serum						

FIG. 12. Case 6. Laboratory studies one year after initial attack.

## Liver Function Schedule No. I

Name R. E. Hospital No. 763482Dates 3-6-46

H <sub>2</sub>		CC=2+				
2.0	2.6			10	10	
1.8	2.4			9	9	400
1.6	2.2			8	8	350
1.4	2.0	16	35	7	7	300
1.2	1.8	14	30	6	6	250
1.0	1.6	12	25	5	5	200
0.8	1.4	10	20	4	4	175
0.6	1.2	8	15	3	3	150
0.4	1.0	6	10	2	2	125
N 0.2	0.8	4	5	1	1	100
0.0	0.4	2	0	0	0	75
				2 days		50
						25
S.B. 1'	S.B. T-1'	T. Units	B. 5 mg. per kilo % at 45'	U.E. Units per 2 hr. spec.	U.U. mg. per 24 hr.	U.C.P. γ per 24 hr.
Mg. per 100cc. serum						

FIG. 13a. Case 7. Laboratory studies three months after initial attack.

Case 7 (R.E. ♀, 38) had suffered from what appeared to be a typical attack of infectious hepatitis, three months previously. In figure 13a it is seen that the proteins were qualitatively abnormal and the bromsulfalein slightly elevated, the urine coproporphyrin considerably elevated, while the serum bilirubin and urine Ehrlich tests were normal. Although not shown here, the cholesterol esters were also well within normal limits. The biopsy revealed an outspoken cirrhosis of the liver (figure 13b). Since this patient

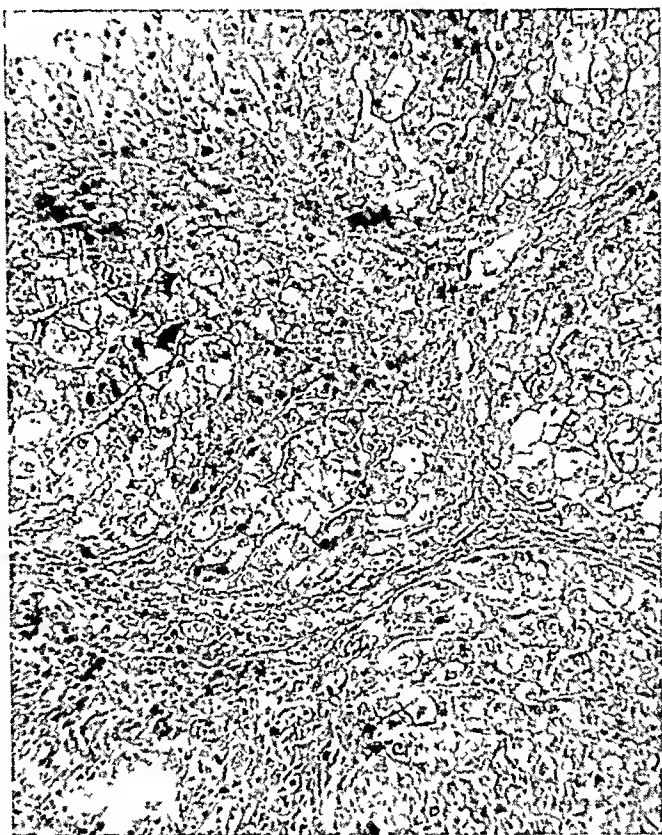


FIG. 13b. Case 7. Photomicrograph  $\times 175$ . Needle biopsy of the liver secured with Vim-Silverman needle March 8, 1946.

had not exhibited any previous signs of liver affection, it is believed that she represents an example of chronic hepatitis undergoing transition to cirrhosis of the liver. This is but one of a number of such transitions that we have had opportunity to study, and which are discussed in more detail elsewhere.<sup>4a, 40, 41</sup>

Figure 14 presents a composite chart of the usual course of events in infectious hepatitis as regards those liver function studies believed to be of most value. Points which may be reemphasized here are (a) the early appearance of bilirubin in the urine together with an early rise of the one minute or prompt reacting bilirubin; (b) an early disappearance of bilirubin from the urine at a time when the serum bilirubin, both prompt and delayed,

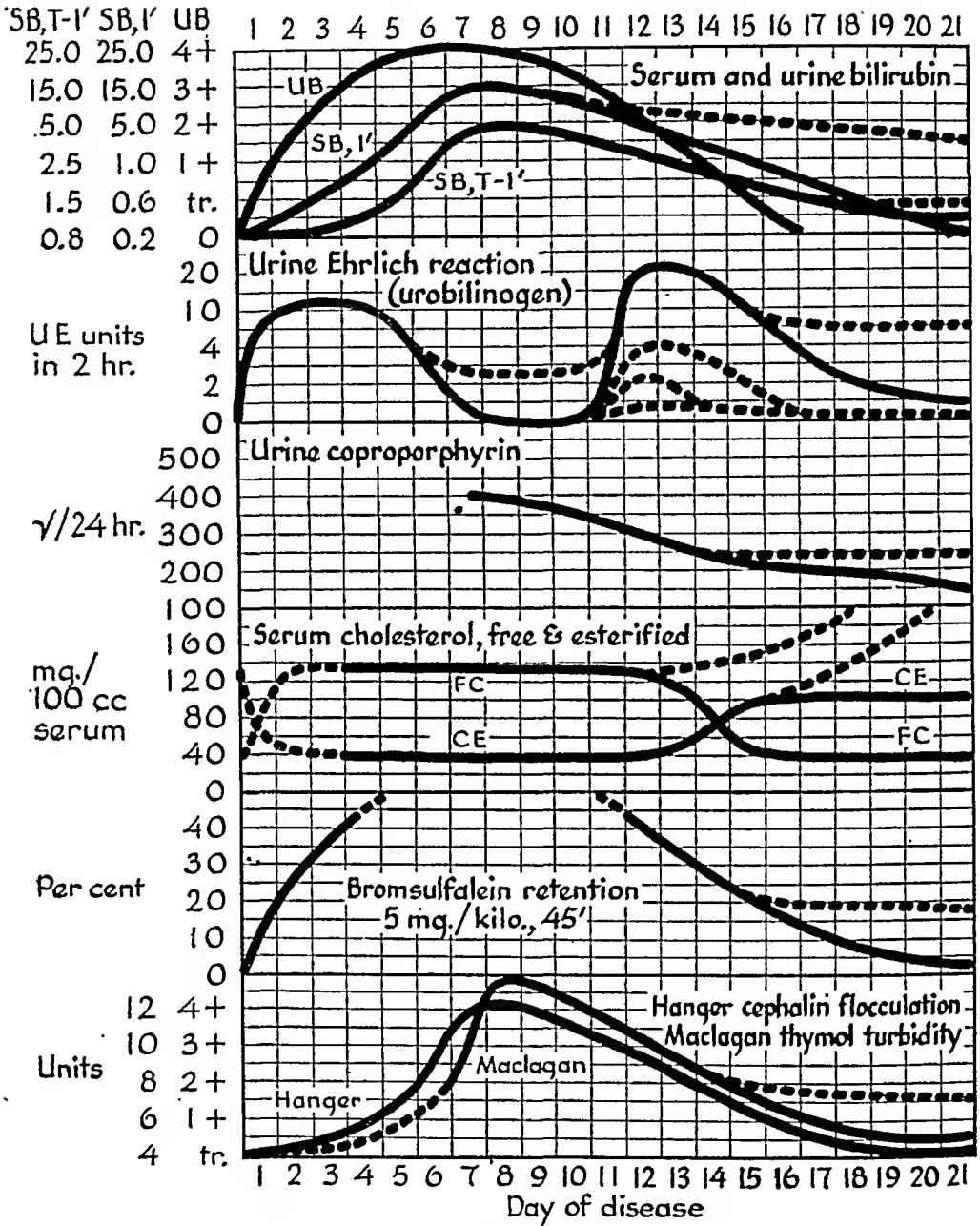


FIG. 14. A composite study of liver function in the different stages of the usual or typical case of infectious hepatitis.

is still distinctly elevated; the broken line indicates the much slower de-fervescence of jaundice observed in some cases, especially those of the cholangiolitic type; in some of these cases, in fact, the jaundice may persist at the same level for months or years; (c) the early positivity of the urine Ehrlich reaction with a characteristic diminution or disappearance during the height of jaundice. The return of urobilinogen to the urine usually heralds beginning improvement, but as noted, the increase in some cases is transitory or not more than slight. The persistence of a positive urine

Ehrlich reaction is believed to indicate that the disease is still active. (d) The same is thought to be true for a persistent elevation of the urine coproporphyrin. Actually the broken line in this instance is more nearly representative of the majority of cases. On the basis of present evidence, which will be discussed in detail elsewhere, the urine coproporphyrin is one of the last to return to normal. (e) From the available information, it is probable that the cholesterol ester percentage declines sharply in the early stage of the disease, the finding being well established by the fourth or fifth day.<sup>7, 44</sup> The percentage of esters is usually very low at the time of the peak elevation of the serum bilirubin.<sup>44</sup> (f) Bromsulfalein retention occurs early and rapidly becomes marked. This was emphasized in the studies of Barker, Capps, and Allen in the Mediterranean Theater.<sup>8</sup> Persistent bromsulfalein retention above 5 per cent after the disappearance of jaundice points to the possibility of continued activity or transition to cirrhosis of the liver.<sup>44, 45</sup> (g) On the basis of our own experience, the cephalin flocculation and thymol turbidity tests agree very well in most cases of hepatitis, although not so well in certain cases of cirrhosis and other affections of the liver. Based on the available evidence, these tests usually do not become positive as early as the others shown. According to Neefe,<sup>46</sup> the Hanger test usually becomes positive before the thymol turbidity. The data of Watson and Rappaport<sup>42</sup> together with further experience in this laboratory, revealed good agreement between the two tests in the defervescent stage of the disease, although occasional instances were noted in which the thymol turbidity was persistently positive after the cephalin flocculation had become negative. Hanger<sup>43</sup> and Hoaglund<sup>47</sup> have observed this with greater frequency, but this difference may be more apparent than real, since both of these investigators used other methods of recording the degree of turbidity than that employed by MacLagan,<sup>34</sup> and by Watson and Rappaport.<sup>42</sup> The question has arisen as to whether the test may be positive as an evidence of immune response, in other words, representing an elaboration of globulin elsewhere than in the liver cells. This question cannot be answered at present, but it has become clear that the test is specific for a certain type of globulin, or globulin lipid complex<sup>34, 35</sup> as it is commonly negative in other diseases associated with hyperglobulinemia.

Finally, it might be well to recapitulate briefly in regard to the procedures believed of most value in the study of liver function in hepatitis. These may be divided into three groups: (1) The incipient or pre-icteric stage: the serum bilirubin, especially the prompt reacting type, the urine bilirubin, and the urine Ehrlich reaction for urobilinogen; (2) the icteric stage: the Hanger and MacLagan tests for abnormal serum proteins, the serum cholesterol, free and esterified, and the urine Ehrlich reaction followed seriatim; (3) the late defervescent stage: the serum bilirubin, especially the delayed reacting type, the urine Ehrlich reaction, the Hanger and MacLagan tests, the bromsulfalein test, 5 mg. per kilo. at 45 minutes, and the 24 hr. urinary urobilinogen and coproporphyrin.

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# THE CLINICAL MANIFESTATIONS OF SICKLE CELL ANEMIA \*

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IN 1910 J. B. Herrick<sup>1</sup> first reported the association of sickle shaped erythrocytes with severe anemia and certain clinical symptoms now recognized as the clinical entity termed sickle cell anemia. In 1923 and 1924 Sydenstricker<sup>2,3</sup> and Huck<sup>4</sup> pointed out its relative frequency. There have been many subsequent articles concerning various features of this disease, but it was thought worthwhile to report the general clinical manifestations as observed in the present series of cases. During the period January, 1936 to January, 1946 there were 48 cases of active sickle cell anemia treated in the medical wards of Kings County Hospital. The clinical manifestations tabulated in this article were those demonstrated by these patients. All patients with sickle cell anemia without active sickle cell anemia have been eliminated.

*Race:* All the patients were of the negro race.

*Age:* The ages given in table I are those at the time of the first admission to the hospital and of the start of symptoms as well as could be determined from the charts.

TABLE I

Age	On Admission	At Onset of Symptoms
0- 4 years	11 cases	15 cases
5- 9 years	6 cases	9 cases
10-14 years	8 cases	5 cases
15-19 years	11 cases	4 cases
20-24 years	4 cases	2 cases
25-29 years	5 cases	
30-34 years	1 case	
35-39 years	2 cases	

*Duration:* The duration of symptoms was very difficult to estimate. Histories varied on different admissions even when they were obtained from the same informant. In this article the indications for estimating duration of disease were (1) a known previous diagnosis of sickle cell anemia, (2) a history of pains suggestive of crisis or a history of rheumatic fever, and (3) a history of ulcers of the legs without other known cause. With these points in the past history the demonstration of active sickle cell anemia during hospitalization was considered to indicate that the previous symptoms were also due to the disease. It is realized that this is a very uncertain method. In many cases the histories were so uncertain that no attempt was made to establish the duration of symptoms.

*Sex:* There were 24 males and 24 females.

*Siblings:* In five cases there was a brother or sister known to have active sickle cell anemia. In addition there were two cases with a questionable history of a brother or sister with this disease. In three of the five cases

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there was a history of two brothers or sisters with active sickle cell anemia. At one time there were twins, age one year, in the ward both of whom had active manifestations of the disease.

TABLE II

## Duration of Symptoms Possibly Due to Sickle Cell Anemia

Diagnosed on admission	11 cases
Duration less than 5 years	11 cases
Duration more than 5 years and less than 10 years	6 cases
Duration more than 10 years and less than 15 years	4 cases
Duration more than 15 years and less than 20 years	4 cases

*Temperature:* It was striking that practically all the patients manifested fever at one time or another. The great majority of the patients had an elevation of temperature during most of their hospital stay, even when they were asymptomatic.

TABLE III

## Highest Temperatures Recorded for Each Patient

Under 98°	1 case
98 to 99°	5 cases
99 to 100°	7 cases
100 to 101°	14 cases
101 to 102°	7 cases
102 to 103°	4 cases
103 to 104°	8 cases
104 to 105°	2 cases

*Pulse:* A tachycardia was the usual manifestation. The pulse of some infants was not recorded.

TABLE IV

## Highest Pulse Rate Recorded for Each Patient

Pulse Rate Per Minute	
Under 70	2 cases
70 to 80	1 case
80 to 90	6 cases
90 to 100	9 cases
100 to 110	2 cases
110 to 120	7 cases
120 to 130	1 case
130 to 140	0
140 to 150	0
150 to 160	3 cases

*Blood Pressure:* The highest blood pressure recorded was systolic 135 mm. Hg and diastolic 80 mm. Hg. This patient showed evidence of nephritis.

*Chief Complaint and Associated Prominent Symptoms or Signs:* The 48 patients had a total of 129 admissions during this period of 10 years. The chief complaint was that symptom or sign which caused the patient to seek admission to the hospital. The associated prominent symptoms or signs were those of major importance to the patient at the time of that particular

admission. There were many other symptoms or signs not listed because they were not considered major by the patient during this particular admission. At another admission they might be listed as the chief complaint. Some admissions were during an asymptomatic stage for transfusion or plastic operation for ulcer of the leg. In that case no chief complaint is listed.

TABLE V

## Chief Complaint and Associated Prominent Symptom or Sign

	As Chief Complaint	As Associated Prominent Symptom or Sign
Joint or extremity pain	32 admissions	17 admissions
Abdominal pain	22 admissions	3 admissions
Ulcers of the legs	12 admissions	4 admissions
Common colds	9 admissions	0
Neuropsychiatric	8 admissions	5 admissions
Weakness	6 admissions	4 admissions
Dyspnea	4 admissions	8 admissions
Swelling of the abdomen	4 admissions	0
Severe epistaxis	2 admissions	2 admissions
Swelling of the legs (no ulcers)	1 admission	4 admissions

TABLE VI

## Findings on Physical Examination

Jaundice	14 cases
Enlarged liver	19 cases
Enlarged spleen	19 cases
Enlarged heart	24 cases
Murmurs of the heart	
systolic—apex	35 cases
systolic—pulmonic area	10 cases
systolic—aortic area	3 cases
systolic—apex and pulmonic areas	8 cases
systolic—apex and aortic areas	3 cases
diastolic—apex	15 cases
diastolic—aortic area	3 cases
Ulcers of legs or scars with history of ulcers of legs	12 cases
Enlargement of lymph glands	
cervical	18 cases
axillary	9 cases
inguinal	8 cases
epitrochlear	1 case
general enlargement	1 case
Fundus oculi (5 cases examined)	
normal vessels	2 cases
tortuous vessels	3 cases

*Ulcers of the Legs:* There were 12 cases on whom ulcers of the legs or scars with histories of ulcers of the legs were observed during their hospital

TABLE VII

## Ulcers of the Legs or Scars with a History of Ulcers

Age on admission	
10–14 years	1 case
15–19 years	5 cases
20–24 years	1 case
25–29 years	2 cases
30–34 years	1 case
35–39 years (both 37 years)	2 cases

stay. On several other cases scars were found, but there was no history of ulcers and they may have been traumatic. The youngest patient with ulcers of the legs was 11 years of age.

*Other Findings of Interest:* There were a number of other findings not listed above. Some are pertinent to this disease and will be discussed in the comment.

TABLE VIII  
Other Findings of Interest

Mental deficiency	7 cases (3 referred to mental institutions)
Priapism	1 case
Salmonella infection	2 cases
Salmonella osteomyelitis	1 case
Turriccephaly	2 cases
Meningitis-pneumococcus type XII	1 case (recovered)
Nephritis	2 cases
Pregnancy (7½ mos. stillbirth)	1 case
Congenital cataracts	1 case
Lymphogranuloma inguinale	1 case
Venereal warts	1 case
Abnormal electrocardiogram other than prolonged P-R interval	1 case

*Roentgenograms of the Bones and Skulls:* About 85 per cent of the roentgenograms of the skull and about 57 per cent of the roentgenograms of the long bones demonstrated changes compatible with sickle cell anemia. In addition there were changes suggestive of blood dyscrasia in the ribs (two cases) and the ilium (one case).

TABLE IX  
Report of Roentgenograms of the Bones and/or Skull: Total 29 Cases

Skull: Normal	14 cases
Changes present	12 cases
Long bones: Normal	14 cases
Changes present	8 cases
Ribs: Normal	no reports
Changes present	2 cases
Ilium: Normal	no reports
Changes present	1 case

*Roentgenograms of Heart:* There were 28 patients concerning whom there was mention of the size and shape of the heart in the reports of their roentgenograms. Of these there were 24 who were found to have evidence of cardiac enlargement. In four cases the heart was reported not to be enlarged. In three cases the condition of the lungs was reported with no mention of the heart. It was not stated whether this was due to technical difficulties or lack of abnormality. Esophograms with barium demonstrated retrodisplacement of the esophagus compatible with enlargement of the auricle in two cases. One of these cases was also interpreted as demonstrating elevation of the left main bronchus. In a third case the esophogram was reported as "suggestive of auricular enlargement." All other cases were negative or an esophogram was not done.

*Electrocardiograms:* There were electrocardiograms reported for 20 cases. Only one showed any abnormality other than prolongation of the P-R interval. In this case the P-R interval was 0.16 sec., there was slurring of the QRS waves, and the T waves were of low voltage in all leads reported. She was a 10 year old girl admitted to the hospital because of an abdominal crisis. There was a history of a transient, painless paralysis of both of her legs for three weeks at six years of age. Examination revealed: pallor; cervical and axillary glands enlarged; heart, enlarged, coupled beats present, systolic murmurs at the pulmonic and apical areas with an inconstant apical diastolic or presystolic murmur. Once there was a report of a questionable murmur of aortic insufficiency; pulmonic second sound was accentuated. Liver described as four fingers'-breadth below the costal margin; spleen described as "down to the iliac crest." Skull and long bones reported normal on roentgen-ray examination. Blood count: hemoglobin 6 grams, erythrocytes 1,600,000, leukocytes 40,000, polymorphonuclears, 70 per cent, 140 nucleated erythrocytes per 75 leukocytes. Icteric index 4.5 units. Sedimentation rate 6 mm. per hour. Report of roentgenogram of the heart: enlarged, mitral contour, hypervascularity of the lung fields. No enlargement of the auricle demonstrated by esophogram. Two facetted gall stones were seen. There were four separate admissions. At the time of her last admission she was complaining of dizziness and pains in her knees of one week's duration. However, this was the only history obtained of pain in her extremities. The only electrocardiogram had been taken during a previous admission.

TABLE X  
Report of Electrocardiograms—P-R Intervals and Ages

P-R Interval	Age	P-R Interval	Age
0.12 secs.	10 years	0.16 secs.	17 years
0.14 secs.	1 year	0.16 secs.	10 years
0.14 secs.	18 years	0.18 secs.	25 years
0.14 secs.	25 years	0.18 secs.	27 years
0.14 secs.	30 years	0.18 secs.	23 years
0.14 secs.	3 years	0.18 secs. }	14 years
0.14 secs. }	6 years	0.20 secs. }	
0.16 secs. }		0.20 secs. }	10 years
0.16 secs.	11 years	0.20 secs. }	
0.16 secs.	14 years	0.23 secs.	16 years
0.16 secs.	4 years		
0.16 secs.	3 years		
0.16 secs.	19 years		

*Blood Counts:* The leukocyte counts are uncertain as the number of nucleated erythrocytes was often large, and the corrected count is probably much lower in those cases with very marked leukocytosis. There were only four blood counts with leukocyte counts below 10,000, and there were 8 leukocyte counts over 30,000. In general there was a moderately severe anemia with a definite leukocytosis, usually without much increase in the percentage of polymorphonuclear leukocytes.

*Reticulocyte Counts:* There were too few reticulocyte counts to be of any statistical value. Those reported were all elevated.

*Icteric Index:* There were many reports of elevation of the icteric index. There were only 10 cases with an icteric index of 5 units or below, and for seven of these other tests were all above normal. There were four reports of

TABLE XI  
Blood Counts

	Lowest	Average	Highest
Hemoglobin	3 grams	6.7 grams	12 grams
Erythrocytes	1,000,000	2,508,000	5,180,000
Leukocytes	5,700	19,382	52,000

over 100 units, the highest being 280 units. Some of these high values will be discussed in the comment.

*Deaths:* There were four deaths with three autopsy reports which will be discussed in a subsequent article.

### COMMENT

Several interesting observations are emphasized by this report. One is the frequency of abdominal pain. Many times this complaint was a difficult problem as has been reported by others.<sup>5</sup> Many diagnoses were considered, including renal colic, acute salpingitis, acute appendicitis, and acute cholecystitis. None of these patients was submitted to operation for abdominal pain.

*Mental Deficiency:* The frequency of mental deficiency is surprising. This diagnosis was made on the basis of clinical observation only, but was borne out by the admission of three of these patients to mental institutions. Although many authors have reported neurological manifestations,<sup>6, 7, 8, 9</sup> mental deficiency was not emphasized as a feature of this disease. Other findings included localized paralyses, signs of meningeal irritation, dizziness, headaches, drowsiness, convulsions, and choreiform movements. Probably future attention to neuropsychiatric manifestations will reveal that cerebral lesions are more common than is generally realized.

*Priapism:* One patient developed priapism. There have been several reports of priapism due to sickle cell anemia, but <sup>10, 11, 12</sup> it is believed that this is the first case reported which was relieved by 150 R.U. of roentgen therapy to the penis. No data are available as to later developments in this case.

*Pregnancy:* This report includes a 17 year old female who was first admitted when she was six months' pregnant. At that time she gave a history of pain in her joints with dyspnea and palpitation of five years' duration, and abnormal movements of her body for a few hours. At physical examination there were choreiform movements of her extremities, but she signed her

release and left the hospital. She was readmitted when she was seven and one-half months' pregnant. At that time she was complaining that for 24 hours she had severe pains in her arms with fever. Examination revealed an icteric tinge to her sclerae, enlargement of her cervical lymph nodes, no clinical enlargement of her heart, but there was a systolic murmur at the apex of her heart, and once a presystolic murmur was heard in the same area. The liver and spleen were not palpable. There were scars on both of her legs. The uterus was the size of a seven and one-half months' pregnancy. Blood count: hemoglobin 6.8 grams, erythrocytes 2,600,000, leukocytes 18,300 (corrected to 12,200), 100 per cent sickling of the blood smear after 24 hours; icteric index 18 and 22 units, van den Bergh direct delayed, faint trace; electrocardiogram was normal (P-R interval 0.16 sec.). After a few days she developed a severe abdominal crisis which continued for several days and did not cease for some time after she suddenly delivered a still born male child.<sup>13</sup>

*Heart:* It is interesting that examination by roentgen-ray revealed cardiac enlargement in 50 per cent of the total cases of this series. Only four or possibly seven cases had no demonstrable cardiac enlargement. It is unfortunate that all cases did not have a roentgenogram of the heart. The reports of enlargement of the left auricle by esophogram are unusual.<sup>14</sup> None of the autopsies revealed valvular damage or myocardial evidence of rheumatic fever.<sup>14, 15</sup>

*Electrocardiograms:* There were five cases which were considered to have prolongation of the P-R interval. Quite possibly more frequent electrocardiograms would have demonstrated more cases with a prolonged P-R interval.<sup>14, 15</sup>

*Roentgenograms of the Bones and Skulls:* Sometimes these changes in the osseous system were scanty and sometimes marked, but all cases suggested blood dyscrasia to the roentgenologist. Several reports<sup>16, 17</sup> of these bone changes are available. No unusual change, not already described, was found.

*Icteric Index:* The icteric index was very variable even in the same patient during the same admission. The two highest, 150 and 280 units, were reported for different patients. The first of these patients was considered to have a hepatitis. The urine was strongly positive for bile; urobilinogen was present; stools were negative for bile; van den Bergh was direct delayed, faint trace; serum bilirubin was 19 mg. per 100 c.c. All symptoms and signs gradually subsided.

The second case also demonstrated a strongly positive test for bile in the urine with urobilinogen present. The stools were negative for bile; serum bilirubin was 10.1 mg. per 100 c.c. A gall-bladder series did not reveal any calculi, but the gall-bladder shadow was faint, and failed to evacuate after a fatty meal. These were both undoubted cases of active sickle cell anemia. Diagnoses of hepatitis and cholecystitis are difficult to prove or disprove without operation or autopsy.<sup>18, 19</sup>

*Liver and Spleen:* One of the most striking features of this study was the marked, rapid changes in size of both the liver and spleen. During the same hospital stay the spleen might be reported as "not palpable," and then "increased to the iliac crest." The liver might suddenly increase in size until it was described as palpable three or four fingers'-breadth below the costal margin. Recession of both organs could also be rapid. Usually during the period of rapid increase in size there would be a notation of abdominal pain with tenderness of the involved organ, but tenderness and pain were not always reported. After subsiding they could sometimes again increase in size. In general the very large spleens were in patients less than 10 years of age, but there was one girl, 19 years of age, with a spleen "enlarged to the umbilicus" who had complained of pain in her legs "all her life." For three years prior to admission she had ulcers of her legs. Four skin grafting operations were performed.

### SUMMARY

The clinical manifestations of 48 cases of active sickle cell anemia are noted and tabulated. All patients with sickle cell anemia without active symptoms have been eliminated.

The previous concepts of the clinical features of this disease are confirmed, but particular attention is directed to the frequent occurrence of the following manifestations: (1) cardiac enlargement, (2) the presence of diastolic as well as systolic murmurs of the heart, (3) prolongation of the P-R interval, (4) roentgenographic changes in the osseous system, (5) rapid and marked changes in the size of the liver and spleen, (6) neuropsychiatric signs and symptoms especially mental deficiency, and (7) abdominal crises.

Two unusual manifestations were the demonstration by esophogram of auricular enlargement in two cases, and the relief of priapism by roentgen therapy.

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# HISTAMINE IN THE TREATMENT OF PEPTIC ULCER \*

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CRUVEILHIER in 1829 said "ulcer of the stomach is surrounded by profound obscurity, and one wonders why a single place in the stomach is deeply affected and all the other parts of the organ are in a state of perfect integrity." Since that date many investigations have been devoted to the study of both the etiology and treatment of ulcer, and have led to numerous arguments and conflicting opinions. The attempts to determine the etiology of peptic ulcer have failed to yield any convincing results. Others have attempted to prevent the development of experimental ulcers by psychological, endocrine or chemical means, particularly by attacking what, in our opinion, seems to be the normal gastric medium of the ulcer patient, *his* acidity. A great many have accepted the view, as expressed by Palmer,<sup>1</sup> that the continued secretion of an abundance of a highly acid juice constitutes the greatest hindrance to healing, or at least that acid is irritating to the ulcer (Sandweiss<sup>2</sup>), and that it contributes to the development of the pain of ulcer (Quigley<sup>3</sup>).

Others have seriously questioned this view. Thus Brown and Dolkart<sup>4</sup> observed no significant change in acidity prior to the recurrence of symptoms of ulcer and believe that the degree of free acidity bears absolutely no relationship to the degree of distress. Barford<sup>5</sup> found the acidity higher after treatment than before. The observations (e.g., by Val Dez<sup>6</sup>) that the volume of nocturnal gastric secretion is greatly increased in patients with ulcer has been questioned.<sup>2</sup> Eusterman and Balfour<sup>7</sup> among many others have noted that sodium bicarbonate depresses acidity only momentarily and that in a few minutes this is at least as high as before the medication. Even section of both vagus nerves causes only a temporary arrest of the secretion of acid. They found that patients who developed marginal ulcer had no higher acidity than those who remained free from recurrence. They also state that under favorable circumstances ulcers have healed permanently without treatment by alkalies, and the majority of patients whose duodenal ulcers were permanently cured after gastroenterostomy continued to have more or less free HCl in their gastric secretion.

This illustrates a few of the contradictory observations and views that have been expressed regarding peptic ulcer. The large number of procedures advised and discarded in the therapy of ulcer attests to the confusion on the subject.

Removal of foci of infection has been advocated by some in the belief that there is a relationship between these foci and the production of ulcer.

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Allergy has been noted as a possible cause and investigation of allergens as a method of treatment has been advised.

The drugs suggested for direct action on the gastric mucosa have been numerous. The bismuth salts have been used for decades. Sodium bicarbonate was employed until stopped by the fear of alkalosis without regard to the fact that the gastric acidity rises after a brief depression. Then came the slower acting antacids like the carbonates and the oxides, and more recently the adsorbent, such as the aluminum salts in various combinations. Belladonna and other antispasmodics have been widely acclaimed. In order to counteract the supposedly vicious nocturnal secretion of acid, milk drip and aluminum hydroxide drip were suggested. Mucin and okra mucin were heralded as the "cure" because of their protective properties. A number of substances have been administered by injection: pepsin, parathyroid and insulin as well as various protein products, and more recently histidine. The latter was advised because of the supposed amino-acid deficiency believed to be present in ulcer patients. Pituitary "snuff" was employed for a short period of time. Because patients who become pregnant lose their ulcer symptoms, the urine of pregnant females was searched for some protective substance. This work led finally to the isolation of urogastrone from normal urine. The mucous membrane of the stomach and duodenum then received the investigators' attention with the elaboration of enterogastrone and duodenal extract. Then came hyperalimentation with protein hydrolysates.<sup>8</sup>

The surgeons also have participated in the fight against recurrent gastroduodenal and, as an occasional sequel, marginal ulcer. They began with simple excision and followed with gastro-enterostomy with or without pyloric occlusion, and later employed pylorectomy and pyloroplasty. Then came partial and more recently subtotal gastrectomy with vagotomy, first unilateral and then bilateral. Now the newest procedure to be advised is vagotomy without gastrectomy.

All of these procedures had but one aim: acidity interferes with ulcer healing, and therefore a way must be found to depress or remove the gastric acidity permanently! At this point it suffices to note merely that, regardless of the procedure advocated, ulcer recurrences kept coming and no method has as yet belied the aphorism: "once an ulcer patient, always an ulcer patient." These are but a few of the many questions which must arise in your minds as they do in ours. Why does the ulcer develop almost always on the lesser curvature of the stomach or in the first portion of the duodenum? What prevents the ulcer from growing deeper and wider after it has formed? Why does the anatomic defect persist although the symptoms of ulcer have disappeared? What is the explanation for the typical ulcer syndrome with negative roentgen-ray findings, and nothing found at operation, which nevertheless was occasionally cured by appendectomy? In what manner is the relief from symptoms so frequently obtained, "after-a-while" as the

result of so many varied methods and procedures, or "in due time" without therapy?

No one can as yet explain why recurrent episodes of symptoms of ulcer generally recur in the spring and fall, or at times after an upper respiratory infection, or frequently following an emotional storm or so often for no apparent reason at all.

We have had the impression for many years, that whereas the acid pepsin factor may be important in the as yet unproved etiology of ulcer, there appears to be no relationship between the maintenance of gastric acidity and the disappearance of either the symptoms or of the anatomic defect or of both.

In complete contradiction, therefore, to the implied dictum: "neutralization of acid is necessary for the treatment of peptic ulcer," we have used histamine, a potent acid-stimulating, vaso-dilating agent, by injection over a period of about eight months. We know that it has frequently been suggested that histamine plays a part in the hypersecretion of gastric juice in the patient with an active ulcer. The literature contains many articles on the production of ulcer in animals by the injection or implantation of histamine. In answer to one investigator, who said that "the ease of production of perforating gastric and/or duodenal ulcer in most laboratory animals by the implantation of histamine in beeswax emphasizes the great importance of the acid activity of the gastric juice in ulcer genesis" we should like to say only this: the doses of the drug used in these animal experiments were enormous and were frequently fatal. Horton<sup>9</sup> had occasion to treat 10 patients with histamine headache and peptic ulcer, in whom both the headache and the ulcer crater disappeared after the injections of histamine he used for desensitization.

Brun<sup>10</sup> in 1944, working on the vascular theory, found that injection of adrenalin in ulcer patients produced an increase of pain which was quickly relieved by nitroglycerin or amyl nitrite without change in the intra-gastric tension. He called attention to the work of Jacob and Israel<sup>11</sup> published in the *Presse Medicale* in 1938, which was first seen by us in March 1946, five months after we had started our study. These investigators reported complete relief from ulcer symptoms in all of 17 cases, using daily injections of 0.1 mg. of histamine. They believed their spectacular results were caused by a change, a relaxation, in the vascular mechanism of the gastro-duodenal area.

In our study we gave an average of 20 daily injections of 0.2 mg. of histamine phosphate to 75 ulcer patients. Except in the few instances in which tincture of belladonna was also used, no other medication was given. Our patients had gastric, duodenal and marginal ulcers. Both sexes were represented, the male predominating in a ratio of about five to one, of whom three males were colored. Some had had one or more hemorrhages just prior to, or at some time before the start of our treatment. The ages varied

from 21 to 65. A number of the cases showed varying degrees of gastric retention, and most of them had been treated on previous occasions by alkalis and non-specific parenteral protein therapy, and two with protein hydrolysates. Several had had perforations at some time in the past. All came to us because they were in the midst of a recurrence of symptoms of ulcer, the number of previous episodes ranging from 2 to 22. The roentgenologic evidence was positive in almost all the cases, a few giving a typical, classical story of ulcer with negative roentgen-ray findings. They were all placed on a liberal, bland diet with frequent feedings, and tobacco was completely forbidden. (It should be noted, however, that some of the patients continued to smoke in spite of our interdiction.) Gastric analysis was done in a number of the patients, and the usual response to histamine stimulation was noted in most.

We have not seen one untoward reaction, even in those patients who had been given 30 or more injections. Of course we did note flushing and temporary headaches at times, especially in the beginning when we gave 0.5 mg. per dose.

If acid, as has been claimed, is irritating to ulcer, in using this powerful acid-stimulating agent we should have found a marked increase in symptoms in these patients who were in what has been called "the active ulcer phase." However, we appear to have seen the opposite, because in but one single instance were the symptoms aggravated. Of the 75 cases treated, complete relief from pain took place after the fourth injection in 50 or 66 per cent of our cases, and in less than 10 injections, in 62 or 82 per cent. An additional 7 or 10 per cent required 12 to 18 injections before pain relief was obtained and five patients or 6 per cent did not respond, the latter even after we had changed our medication to alkali, belladonna and sedation. One patient developed a fatal perforation and hemorrhage during the treatment, and still another perforated soon after we had begun our injections. Several gastric ulcers disappeared rapidly, one in less than three weeks. Gastric retention was relieved in five cases without the use of belladonna, and one had almost complete relief from his concomitant cardiospasm.

Many of our patients have already remained free from symptoms for a period of months, a few in spite of upper respiratory infections and emotional upsets. Eighteen of these were given a second series of injections in the hope that a recurrence could be prevented. We can report that almost all of these patients, who had previously had two or more episodes per year, have now for the first time in years gone through a spring season completely free from ulcer pain. If this small number of cases is any indication at all, perhaps we have found a way to prevent seasonal recurrences.

It must be remembered that gastric ulcers especially have disappeared spontaneously, or in spite, rather than because of a particular form of treatment (although perhaps not until now in the presence of stimulated gastric acidity). One must not use partial or even complete remission from

symptoms for any length of time as the criterion for "cure," as we have all seen both recurrent episodes and remissions after every conceivable type of medical routine and surgical procedure.

It would appear that we might use but two criteria for the evaluation of the results of therapy. Have we obtained rapid relief from the pain of ulcer and can we prevent the recurrences previously experienced? Our work indicates relief of ulcer pain in a large percentage of our cases with startling rapidity and apparent prevention of recurrence in a substantial number. We believe that our work proves that maintenance of gastric acidity does not interfere with symptomatic relief in any, nor with the disappearance of roentgen-ray evidence in some cases. The mechanism of the pain of ulcer may lie in vascular spasm, and its relief may be the result of a change in the mechanism by the use of histamine, regardless of gastric acidity.

### SUMMARY

1. Seventy-five unselected cases of ulcer, with gastric, duodenal and marginal deformities were treated by daily injections of histamine. Only tincture of belladonna was permitted in a few cases.

2. In 66 per cent of the cases, relief of pain took place after the fourth injection, and in 82 per cent after the tenth. Ten per cent of our cases remained unaffected even after 30 injections.

3. The deformities of duodenal and marginal ulcers showed great improvement in some cases, and gastric ulcer was seen to disappear quickly.

4. Twenty-six cases were protected against an anticipated recurrence by seasonal prophylactic injections.

### DISCUSSION

One might ask with propriety, where are the controls? Isn't it possible that injections of sterile water might have produced the same effects? Sterile water, however, would not increase gastric acidity nor would it relax vascular spasm and increase splanchnic blood supply. We have given injections of novoprotein, vaccineurin, pepsin, parathyroid and histidine without adequate results.

If one can take a similar series of more than 100 unselected cases of gastric, duodenal and marginal ulcer, many of whom had had previous hemorrhages and some of whom had had perforations, and obtain complete relief from ulcer pain in four out of five in 10 injections; and if one could take 26 of these and repeat the series of injections with sterile water and prevent anticipated recurrence of ulcer, then one would be justified in saying that the acid-pepsin factor as a possible cause for ulcer recurrence and all attempts at the treatment of the recurrences by the decrease or abolition of gastric acidity by any method (ought to be respectfully interred and laid to rest for all time to come) can be permanently dismissed from consideration.

## CONCLUSIONS

1. Maintenance and even increase of gastric acidity has no bearing on the symptom-complex of ulcer or the disappearance of ulcer deformity.

2. There is no relationship between the continuance of the anatomic deformity and the recurrence of ulcer.

3. The mechanism of the pain of ulcer seems to be vascular and is relieved by the injection of histamine which relaxes vascular spasm and increases splanchnic blood supply.

4. It appears possible to prevent recurrences by prophylactic seasonal injections of histamine.

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# CONTINUOUS FEVER OF INTESTINAL ORIGIN\*

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No phase of medicine is more fascinating, no problem in the clinical sciences more elusive than the picture of low-grade continuing fever that defies elucidation. Many interesting theses have been written upon this topic, among the most important and recent being those of Hamman and Wainwright<sup>1</sup> in 1936, Kintner and Rowntree<sup>2</sup> in 1934, and of Reimann<sup>3</sup> in 1936. In these various treatises one reads of possible causes of such fever, causes which are recognized in classical medicine, such as tuberculosis, syphilis, rheumatic fever, tularemia, brucellosis, pyogenic infections, bacterial endocarditis, Hodgkin's disease, new-growths, and fevers of psychogenic origin. In none of these thorough and exhaustive papers is there a hint that the intestinal tract may be the site of the causative factor of obscure low-grade fever.

In our clinical experiences we have encountered such cases in which the subjective symptoms of abdominal pain and mild diarrhea have escaped notice and emphasis. We are impelled to call attention to a group of cases in which obscure fever has ultimately been explained by the discovery of benign inflammatory disease in the small or large bowel. Distal or general manifestations have as a rule similarly been ignored or misinterpreted, ocular complications, articular involvement and cutaneous rashes have failed to be appreciated in their relationship to the fever and to the mild diarrhea, the whole making a symptom-complex which is easy to recognize when the significance of the symptoms as a whole is appreciated.

*Ulcerative colitis* of the non-specific variety is a common source of low-grade fever, and it is recognizable with ease because the severity of the diarrhea, the abdominal pain and the loose fluid movements readily focus attention upon the intestinal tract. The diagnosis is easily verifiable by a sigmoidoscopic examination and a roentgenographic study following a barium enema. Complications in the large or smaller joints of the extremities are not uncommon, the so-called "arthritis dysenterique" and ocular complications and cutaneous rashes are not unusual.

Yet, obvious as such a case should be to an experienced general clinician, we encountered an instance in a young woman who was treated for keratitis and episcleritis with low-grade continuous fever, competent ophthalmologists in charge of the case focusing all attention upon the obvious ocular lesions and failing over a course of years to take into consideration the mild but obvious diarrhea which was not pressed upon their attention. Eventually sight was lost in both eyes owing to corneal opacities resulting from healing keratitic ulcerations. The continuous low-grade fever and the low leukocyte count were readily shown by barium enema and sigmoidoscopy to originate in a severe ulcerative colitis involving the whole of the colon. The ocular manifestations were but complications of the intestinal infection.

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*Segmental Colitis:* A most characteristic type of low-grade fever of intestinal origin with minimal local symptoms but with maximal general manifestations is often seen in cases of regional or segmental colitis. We speak often of this type of case as "right-sided" colitis because the cecum, ascending and transverse colon are most often involved, whereas the sigmoid and, particularly the rectum are spared. The freedom of the rectum and anal sphincters from involvement explains the mildness of the diarrhea, perhaps only two to three stools per day without urgency but accompanied by mild abdominal pain. This type of disease is further notable for systemic manifestations, such as continuous low-grade fever, and a low leukocyte count; and for involvement of large joints such as knee, elbow, wrist, as well as the temporo-mandibular, and the smaller phalangeal and tarsal joints: Notable too are the varied ocular complications, the most common of which are keratitis, corneal ulcerations, phlyctenular conjunctivitis, iritis, and uveitis. The cutaneous manifestations of erythema nodosum and the mucosal involvement in the form of oral aphthous ulcerations may be minimal and easily overlooked.

When, as is usual, the intestinal symptoms of diarrhea and pain are minimal, when the continuous fever and prostration are most noteworthy, and when attention is focused on articular and ocular manifestations, the diagnosis may well go askew. Rheumatic fever is the favorite working diagnosis, bacterial endocarditis, Libman-Sachs disease, and peri-arteritis nodosa are frequently assigned as tentative explanations of the continuous low-grade fever.

A young woman was seen suffering from fever, uveitis and iritis and large swollen joints. The tentative diagnosis was either peri-arteritis nodosa even though eosinophilia and renal manifestations were absent, or disseminated lupus erythematosus without the rash and without cardiac involvement. Throughout the illness the mild diarrhea had been completely overlooked. Eventually the triad of fever, joint involvement and ocular manifestations with an associated diarrhea called for studies to elucidate the cause of the frequent bowel movements. A barium enema readily disclosed a segmental or right-sided colitis. Appropriate treatment of the intestinal infection by chemotherapy and antiseptic lavages led to prompt general recovery, subsidence of fever and rapid amelioration of the ophthalmological manifestations. A similar case, in a young girl, was seen again with low-grade fever, articular manifestations, a corneal ulceration, but in this instance with evidences of an old valvular heart disease in the nature of a mitral insufficiency. The diagnosis of chronic rheumatic heart disease seemed obvious and lesions of the eye and joint as natural complications. All attention was focused on the general manifestations, while the mild diarrhea was completely overlooked. The negative sigmoidoscopy at first discouraged the correct diagnosis, but the barium enema disclosed a typical right-sided or segmental colitis involving the cecum and ascending colon. Again attention to the intestinal infection led to prompt recovery; the corneal ulcer healed readily but unfortunately with a dense opacity obscuring vision in the one eye.

A great many cases of this type of segmental colitis are associated with old valvular heart disease apparently of long standing. The relationship between ulcerative colitis of this type and chronic valvular disease of the heart



will bear greater scrutiny. It may well be that the co-existence of non-specific colitis and rheumatic endocarditis is purely fortuitous in these cases, and yet such a coincidence seems unduly frequent. It would seem that the chronic cardiac involvement occurs more frequently than chronic rheumatic heart disease in the control population for even these climates. Positive blood cultures in ulcerative colitis are not infrequent though the organism found is usually non-specific and is rarely the same bacterium in a successive group of cases. Certain it is that sub-total colectomy cures and removes the colitis and results in subsidence of the active phases of the heart disease with the complete disappearance of all articular manifestations. In most of these cases the low-grade fever subsides when the correct diagnosis is established and attention is focused on the intestinal origin of the infection. Until we meet with our first autopsy in a case of segmental colitis and the heart musculature is serially sectioned for Aschoff bodies, the true relationship of this type of colitis to the heart complications so frequently encountered must remain undecided. The eye and joint complications and the frequent involvement of the heart valves lead to the most common mistake of grouping these cases as chronic rheumatic fever. At times the articular manifestations are so brisk and active that as in one instance the case was referred for study by an orthopedist as one of acute infectious arthritis. The occurrence of a peri-anal abscess for the first time focused attention upon the diarrhea which had been of minimal intensity. The diagnosis of diffuse segmental colitis was readily established by the barium enema. Here medical treatment was unsuccessful in allaying the disease, and operation eventually was required.

When erythema nodosum covers the anterior aspects of the legs and arms the usual diagnosis of rheumatic fever seems well substantiated as part of the low-grade continuous fever, and yet typical erythema nodosum is a very common manifestation of all varieties of ulcerative colitis, it is characteristic of the disease and is moreover a good prognostic sign of eventual recovery.

*Regional Ileitis:* It is interesting to note how frequently the diagnosis of ileitis is completely overlooked in the absence of severe pain and diarrhea and in the presence of continuous low-grade fever.

Such a typical instance was noted in the case of a 12 year old girl whose previous history was negative, except for scarlet fever. Fourteen months previously she developed fever and mild diarrhea, the stools being loose, not bloody and not accompanied by pain. For three months she had been hospitalized for careful observation, the temperature (oral) ranging between 99.6° and 101.1° F. The sedimentation rate was prolonged, secondary anemia (60 per cent hemoglobin) and a mild leukocytosis (12 to 14,000 white cells) were present. The barium enema was reported as showing an "irritable colon," and all other indications of an intestinal origin of the fever were henceforth dismissed. A working diagnosis of rheumatic fever was retained. She continually lost weight but developed some slight tenderness in the lower right abdomen. A negative sigmoidoscopic report lent renewed assurance to the fact that the diarrhea was inconsequential as the cause of the fever. Belatedly a roentgenographic examination after a barium meal revealed a typical terminal ileitis involving 18 inches of the distal ileum proximal to the ileo-cecal valve. Laparotomy confirmed the findings; a resection of the terminal ileum and ascending colon resulted in an eminently satisfactory cure.

In another case seen within the last month a boy of 17 ran irregular fever, at intervals, for seven years. The strictest cross-questioning elicited only one transient period of diarrhea for a few weeks, followed the remainder of the time by normal daily evacuations or by mild constipation. Any number of tentative diagnoses for the irregularly recurrent fever were suggested, the most prominent one being brucellosis, though all blood agglutination and skin tests were negative. Finally a barium meal was given which revealed a diffuse inflammatory involvement of the upper ileum and the lower jejunum in a granulomatous process. The inability to make the correct diagnosis in this case is readily understandable since in the absence of diarrhea, fistulae, perirectal abscesses or distal joint involvement, there was nothing to focus the attention of the observer on the small or large intestine as a causative focus of infection.

*Diffuse ileo-jejunitis* presents a baffling clinical picture, which is little known and rarely recognized. Here, except for the mild abdominal pain and minimal diarrhea, there are no distal manifestations, no articular involvements, no ocular symptoms, no internal or external fistulae, no suppurative rectal complications. Only fever of an irregular and continuous type, secondary anemia and progressive loss of weight mark the protracted clinical course.

A young woman 26 years of age had had an appendectomy performed 15 years previously for what appeared to be a classical instance of acute appendicitis, although no pathological examinations were reported at that time. She was well until 13 years ago when she developed erythema nodosum over the anterior surfaces of her legs, a manifestation which was regarded as rheumatic in origin. Three years ago she began to exhibit fever, low-grade, continuous but at times up to 104.6° F. The erythema nodosum recurred, and six months later for the first time she complained of sharp abdominal pain, usually at night, not associated with meals nor with frequent bowel movements. At no time did she have diarrhea; her weight increased rather than diminished. Her blood count was within normal range and agglutination tests for brucellosis were repeatedly negative. After all these varied years of observation the abdominal pain finally centered attention on her intestinal tract. A barium meal disclosed a diffuse ileo-jejunitis involving almost all of the jejunum and the whole of the ileum down to but not including the terminal segments of the small bowel. The entire small intestine seemed converted into one continuous "string sign" traversing the abdominal cavity from side to side in rigid unyielding loops whose mucosal pattern was obliterated. Exploratory laparotomy was halted at the very last moment by the hitherto unexpected radiographic findings. Subsequently the patient developed a phlyctenular conjunctivitis which with the erythema nodosum characterizes this disease. Under sulfasuxidine and sulfaphthalidine oral therapy, fever has disappeared and abdominal pain has ceased except for occasional slight periodic recurrences.

Many instances of this type of fever due to ileo-jejunitis have been encountered. It is of interest to note the interval between the onset of the fever and the eventual recognition of the cause. This is largely so because the diarrhea is usually so slight, although abdominal pain is commonly present and should be significant. If diarrhea is present the cases are occasionally mistaken for sprue, although the existence of fever should readily differentiate the two diseases. The most common mistake is to accept brucellosis as a working diagnosis.

In our early experience with ileitis we encountered a case of continuous fever of long duration (some years), which because of a positive agglutination test for brucella although in low titer was reported<sup>4</sup> as one of continuous fever due to brucellosis with the "unusual feature of unexplained roentgenographic changes in the distal ileum." After the appearance of the first publication upon regional ileitis, the original physician recognized the true origin of the fever and the real nature of the case, and the diagnosis of terminal ileitis was confirmed at operation.

*Differential Diagnosis:* In general, these cases of low-grade continuous fevers with minimal diarrhea and abdominal pain, particularly when complicated by ocular manifestations, articular involvement or by erythema nodosum, are overlooked because they so closely resemble rheumatic fever, subacute bacterial endocarditis, lupus erythematosus disseminatus (Libman-Sachs disease) or brucellosis. The occasional presence of slight eosinophilia makes the suggestion of periarteritis nodosa all the more likely. The not infrequently associated chronic valvular disease of the heart, plus the articular involvement and the erythema nodosum constitute a syndrome which simulates rheumatic fever very closely. If in addition, as in one case, one observes the onset of an acute endocarditis, with a systolic murmur of daily increasing intensity and high fluctuating temperatures, with negative blood cultures, the similarity to acute rheumatic fever is most startling. The rapid subsidence under penicillin and sulfasuxidine and the eventual cure of the condition by ileo-transverse colostomy, short-circuiting the diseased terminal ileum and ascending colon, removed any doubts as to the origin of the fever, the endocarditis and the articular manifestations. Only by the most careful clinical observations and laboratory tests can these cases of continuous fever of intestinal origin be differentiated from Hodgkin's disease, from subacute bacterial endocarditis, from diffuse lupus erythematosus without the characteristic facial rash. The diagnosis rests upon the proper evaluation of the abdominal symptoms of pain, cramps and diarrhea, no matter how slight, and the utilization of roentgenography for the eventual recognition of the causal pathological factor.

Needless to say, the fluoroscopy and the reading of the roentgenograms must be undertaken by an expert in this field, and adequate time and patience should be devoted to studying the hourly films if they should be indicated because of the nature of the case.

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## IS THERE AN INTRINSIC ASTHMA? \*

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THE classification of patients with bronchial asthma into two groups, namely, extrinsic and intrinsic, was first advocated by Walker<sup>1</sup> in 1918. When the patients exhibited positive skin reactions, the disease was supposedly associated with external causative agents; in patients with negative reactions, so-called intrinsic causes, especially sensitivity to bacteria, were held responsible. Rackemann<sup>2</sup> reported in 1927 that among 1,074 asthmatic patients there were an equal number of extrinsic and intrinsic cases. These investigators did not enlarge upon the clinical manifestations or pathological lesions in order to substantiate their classification which is accepted by most authorities. Since less reliance is now being placed on skin tests, the number of patients termed intrinsically asthmatic has decreased. Nevertheless, there are few textbooks, medical meetings, case reports upon asthma, or patients' hospital records in which emphasis is not placed on this distinction.

Cohen<sup>3</sup> has recently lent his support to this classification. In fact, he has attempted to establish the clinical syndrome of "intrinsic asthma" by setting down the following criteria: "Characteristically intrinsic asthma begins at about 40 years of age with a dry, spasmodic cough," gradually developing into wheezing. "Nasal symptoms are much less common than in cases of extrinsic asthma, although nasal and sinus polyposis are common findings. Skin tests with common allergens are uniformly negative. Environmental control in filtered air is not followed by complete relief from symptoms. Many intrinsic asthmatics are allergic to drugs such as acetyl salicylic acid." Cohen emphasizes the constancy of the attacks and the tendency to permanent tissue changes namely, emphysema, cylindrical bronchiectasis, hyperplastic sinusitis, nasal polyposis and periarteritis nodosa. He notes a high blood eosinophilia and the fact that this syndrome is responsible for the high death rate in asthmatic patients over 40 years of age.

An analysis of this description does not reveal any apparent difference from "extrinsic" asthma with the exception perhaps that the skin tests are "uniformly" negative and that the onset of the condition occurs at about 40 years of age. The description is otherwise typical of true allergic asthma regardless of its cause. There is no apparent reason why patients with nasal and sinus polyposis are relatively free from nasal symptoms, nor is it clear why bronchial asthma which is aggravated or caused by drugs should be termed "intrinsic." No pathological basis for this syndrome is offered nor are there any typical cases recorded in the literature. The concept is weak-

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ened by the introduction of a third group, namely "combined extrinsic and intrinsic asthma," of which Cohen distinguishes two sub-groups, namely "the primary intrinsic with extrinsic complications," and vice versa.

The most significant point brought out by Cohen, however, is the utter hopelessness with which he views the existence of intrinsic asthma. He speaks of the "waste of the physician's time and the patient's money" if intrinsic asthma is not recognized. Such a conception is actually shared by many, perhaps by most, leading allergists. It cannot fail to have serious consequences. Indeed, I have seen patients in whom treatment has been abandoned because their asthma was defined by the physician as "intrinsic." Such an attitude by the physician necessarily creates a great deal of despondency in the patient.

A thorough investigation on this subject is indicated because the concept of the term intrinsic asthma is so deeply rooted in the minds of most clinicians that it interferes with effective treatment. The following questions will be taken up:

1. Is intrinsic asthma a clinical syndrome?
2. Are there exclusively intrinsic or extrinsic causative agents which justify the uses of the terms intrinsic or extrinsic?

Before discussing these questions, brief reference should be made to the establishment of the diagnosis of asthma. In diseases other than asthma in which the causes are difficult to identify, such terms as "idiopathic" or "intrinsic" have been utilized. It is indeed tempting to apply such a term to those cases of asthma in which skin tests do not yield satisfactory data and in which the course appears at present to be hopeless. Three groups of diseases are encountered in which diagnostic problems arise and to which the term intrinsic may wrongly be applied: The first column of table 1 lists the conditions simulating allergic asthma out of a total of 1,442 patients with asthma. Some had been referred with the diagnosis "asthma," while others had actually been treated in my office for some time for "asthma" until further observation resulted in the proper diagnosis. The failure to respond to allergic management in patients who do not exhibit satisfactory skin tests should suggest the possibility of a faulty diagnosis. The second column of this table presents some of the unusual complications of allergic asthma, the presence of which may account for diagnostic and therapeutic difficulties and thus suggest the diagnosis of intrinsic asthma. The third column records true allergic asthma as combined with other conditions which may tend to induce wheezing and which might make asthma appear intrinsic. Probably the most impressive case is that of a 36-year old woman, Mrs. W. N. (case 5) with typical allergic asthma and completely negative roentgen-ray findings who failed to improve until a paralysis of both vocal cords due to injury of the recurrent nerves from a former thyroid operation was properly diagnosed and surgically corrected.

TABLE I  
Conditions Encountered of "Wheezing—that is not asthma" in 1,442 Cases

1. Non-allergic wheezing simulating allergic asthma		2. Complications of allergic asthma		3. Conditions coincident with allergic asthma	
Chronic bronchitis	18	Permanent bronchiectasis	7	Active tuberculosis	2
Tuberculosis	12	Chronic pneumonitis	3	Paralysis of both recurrent nerves	1
Pulmonary carcinoma	5	Loeffler's syndrome	3	Substernal goiter	1
Cardiac decompensation	4	Cystic degeneration of lungs	2	Pulmonary syphilis	1
Aortitis	3	Spontaneous pneumothorax	1	Benign tumor in hilar region	1
Cystic lungs	3	Atelectasis of one lobe	1		
Monilia infection	3				
Pneumoconiosis	2				
Spontaneous pneumothorax	2				
Goiter	2				
Foreign body in bronchi	2				
Pancoast tumor	1				
Esophageal stricture	1				
Pulmonary abscess	1				
Total	59		10		6

### I. SYNDROME OF INTRINSIC ASTHMA

In order to determine whether or not there is a syndrome of intrinsic asthma, a search of our records was made for patients whose signs or symptoms would fulfill all or some of the criteria of this syndrome. From a total of 1,442 asthmatic patients seen from 1942 to 1945, 323 cases were selected because they had chronic, perennial asthma and had been observed sufficiently long to permit proper evaluation of their disease.

1. *Age of Onset:* Since the age of onset was thought to be a determining diagnostic feature, the 323 patients were grouped into four categories (table 2). No noticeable difference was observed in the various age groups in the severity and chronicity of the attacks or with respect to the development of complications. Considering, however, the ages at which they were first seen, it was striking that infants and young children manifested by far the most severe symptoms. The attacks were associated with considerable shock and often followed by pneumonitis. They responded least to the ad-

ministration of epinephrine and aminophyllin, while Benadryl was of greater value in these patients than in the older individuals. Because of the febrile course from the penumonitis and because skin reactions were often negative at this stage, these conditions may be regarded as being of bacterial origin and thus be termed intrinsic. However, previous observations<sup>4</sup> indicate that such attacks were actually due to the common allergens. As these

TABLE II  
The Skin Reactivity and the Results of Treatment in Relation to the Ages  
for 323 Chronic Asthmatic Patients

Age of onset	Total	Skin reactivity			Results					
		Very strong	Positive	Doubtful and negative	Well	Improved	Stationary	Worse	Died	Data insufficient
0-20	158	11 (7%)	113 (72%)	34 (21%)	20 (13%)	102 (64%)	15 (9%)	2	1	18
21-40	87	5 (6%)	63 (72%)	19 (22%)	7 (8%)	58 (67%)	10 (11%)	1	—	12 (13%)
41-60	74	6 (8%)	50 (68%)	18 (24%)	4 (6%)	41 (55%)	14 (18%)	3	4	8 (10%)
61-80	4	—	3	1	—	2	—	1	—	1
Total	323	22 (7%)	229 (70%)	72 (23%)	31 (9%)	203 (63%)	39 (12%)	7 (2.3%)	5 (1.7%)	39 (12%)

children grew older, the febrile and "infectious" character gave way to the usual picture of allergic asthma, in most instances assuming a seasonal aspect and becoming much less severe and frequent.

2. *Negative Skin Tests:* Among the 323 cases, 22 (7 per cent) gave very strongly positive skin reactions; 229 (70 per cent) definitely positive; and 72 (23 per cent) reacted doubtful and negative to intracutaneous skin tests. According to table 2, the skin reactivity is approximately constant in the various age groups. It was generally observed that patients exhibiting strong reactions responded to treatment more readily than others; yet, several individuals with minor positive and questionable reactions, improved considerably when the results of these doubtful tests were made the basis for the allergic treatment. Table 2 demonstrates that there were very few of the 323 patients who fulfilled all three criteria of intrinsic asthma discussed so far, namely: constant attacks, onset at about 40, and negative skin reactivity.

3. *Complications:* An effort was made to determine whether or not the syndrome of intrinsic asthma could be detected more readily among those individuals whose asthma was complicated by secondary changes than in those without complications. It is difficult to present statistical evidence on this point. The three most common complications of allergic asthma, bronchiectasis, sinus infection and pneumonitis, often occur at the height of an asthmatic attack and disappear after its subsidence, during a time when the patient is being treated by his physician rather than studied by an allergist. In bronchiectasis, with the use of penicillin and the employment of frequent bronchoscopic aspirations in conjunction with allergic manage-

ment, improvement usually follows provided that the lesions are due to allergic causes and are not too far advanced. Seven patients had what appeared to be chronic bronchiectasis, three of whom died. In all seven, in addition to the presence of chronic infection, extrinsic causes were demonstrable by skin tests.

Practically every patient manifested some degree of sinus disease at some time. Indeed, the persistent absence of sinus involvement should make one question the diagnosis "allergic asthma." The extent of polypoid degeneration of the nasal membranes and the presence of secondary infection varied with seasonal influences and with the effectiveness of the treatment. In five rather advanced cases of asthma, such extensive changes were present that surgical treatment was necessary, and was followed by improvement of the asthma. When sinus infection dominates the clinical picture, the classification "intrinsic asthma" is particularly suggestive. However, in these five cases, there was sufficient evidence to prove that the infection was superimposed upon allergic changes.

In 12 of 19 asthmatic patients with heart disease, the cardiac history antedated the onset of asthma. In only two of the seven remaining patients an etiological relationship of the heart disease with the asthma appeared possible. Their asthma was proved to be due to extrinsic causes. Incidentally, Mrs. W. H. (case 68), the patient whose asthma had been of the longest duration (65 years) showed no evidence of heart disease. In the other, less common, complications listed in table 1, column 2, asthma on the basis of allergy was definitely established and skin tests were positive. Every one of these individuals was afflicted with extremely severe and chronic asthma, yet treatment benefited even the patients with such "intractable" conditions as the two individuals with cystic degeneration of the lungs.

4. *Refractoriness to Treatment*: Since this constitutes another criterion of the syndrome of intrinsic asthma, an analysis of those patients whose condition deteriorated or who died may yield further information.

Before presenting this analysis, it is necessary to dwell briefly on a few essential points concerning the treatment which differs to some extent from that generally employed. In my experience, chronic perennial asthma consists of a series of acute exacerbations. These usually coincide in summer with the peaks of the three pollen seasons; in winter with the prevalence of bacterial infections, with the prevalence of fungi in the air, and, with the beginning of the heating of homes (house dust!). Treatment is therefore primarily directed toward hyposensitization on a perennial basis against these principal antigens, while diet and other eliminative measures play a secondary part except where there are clear-cut indications for their use. When infections are prevalent, use is made of penicillin and sometimes of sulfonamides. In practically all chronic cases, we avail ourselves of the great benefits derived from repeated blood transfusions and from what is probably the most effective measure, repeated bronchoscopic aspirations of mucus, as outlined elsewhere.<sup>5</sup>



Table 2 reveals seven patients whose disease was progressive and five additional ones who died. In four of the seven cases (cases 8, 39, 40, 56), the diagnosis of allergic asthma might be questioned. There was evidence on roentgen-ray of chronic inflammatory processes in the lungs, which in two cases (cases 8 and 56) represented foci of healed tuberculosis; in the two others, chronic pneumonitis was present in the lower portions of the lungs. These conditions may or may not have been the source of their wheezing. The remaining three cases were the only ones encountered to which one might possibly apply the term "intrinsic asthma." In spite of the most thorough clinical observations no clues as to the cause of the disease were detected:

Mr. J. T. (case 279), 34 years of age, had had chronic wheezing and cough which began shortly after birth and was more pronounced during the winter months. This condition began to be much more severe at the age of 32. Since then the attacks had occurred daily. The patient had otherwise been in excellent health. There were no febrile episodes at any time nor were there any symptoms referable to nasal involvement. There was a family background of asthma: no sensitivity to any antigen was detected by the history. The physical examination, roentgen-ray investigations of the chest and sinuses, including lipiodol studies of the lungs, bronchoscopic examination and laboratory studies revealed no unusual findings other than slight emphysema, the characteristic asthmatic wheezing throughout the lungs and some thickening of the mucous membranes of the sinuses. The intracutaneous skin tests were negative. During the two year period while the patient was under observation, this condition was resistant to every type of treatment employed. He recently moved to California for "a change in climate" from where he reported no improvement.

Mr. K. W. (case 235), aged 35, developed attacks of asthma of a rather unusual pattern at the age of 22. In addition to occasional wheezing in the morning and upon exertion, severe seizures occurred two to three times a year. They were always preceded by what appeared to be an upper respiratory infection with marked rhinorrhea and the production of very large amounts of watery sputum. At the height of the attacks, extreme shock, fever and leukocytosis were present. During these attacks, the chest findings showed characteristic evidence of bronchial asthma, but neither epinephrin, aminophyllin, nor Benadryl was of any avail. Sulfonamide drugs and penicillin, which were administered because of the fever, were of no benefit. The patient, who has been under my observation for 12 years, had been free from attacks during a period of three years after he had received several blood transfusions (Waldbott<sup>5</sup>). Subsequently, however, the attacks recurred.

Miss M. W. (case 286), aged 29, had asthmatic attacks which came on gradually at the age of 19. They usually occurred at night and often required injections of epinephrin (0.1 to 0.2 c.c.). There was no family background of allergy nor was there a history of sensitization to foods, animals, etc. In addition to the findings of bronchial asthma in the lungs, the patient was considerably underweight. The chest findings were those encountered in uncomplicated bronchial asthma. The patient has coöperated fully for four years. She has been subjected to repeated laboratory and roentgen-ray studies and rhinological and bronchoscopic investigations which revealed nothing unusual. There has been no effect on the course of the disease from all the therapeutic measures employed other than a five-day period of complete freedom from attacks following injections of milk and a similar period after the administration of large doses of iodides and stramonium. Interestingly enough, during the

past year she exhibited rather strong reactions on intradermal skin testing, whereas these tests had been entirely negative on three previous occasions when carried out with the same technic.\*

There is no question but that these patients present serious problems, both for diagnosis and treatment. In some, there may have been pathological changes other than those due to allergy. In the others, the clinical picture varies so greatly in each case that it is impossible to group them into a single clinical entity. There are certainly no common denominators with respect to age of onset, skin reactivity, or progress. This point is further elucidated by an analysis of the fatalities.

5. *Fatalities*: All five patients who died had been clinically sensitive to extrinsic substances and had given strongly positive skin reactions.

Three presented bronchiectasis, which was associated in one case, Mr. J. McC., aged 60 (case 320), with advanced cardiac damage. Another of the three, Mr. W. F., aged 52 (case 261), had for several months improved considerably, having especially benefited from penicillin and repeated bronchoscopic aspirations. He died very suddenly during a coughing spell at night in a manner suggesting that mucus might have obstructed one of the main bronchi.† The autopsy showed some bronchiectasis. The fourth fatality was Mrs. J. L., aged 42 (case 196) with the diagnosis thrombo-angiitis obliterans manifesting hypertension, chronic nephritis and diabetes. Although her skin tests had been markedly positive, she had never shown improvement from any treatment during the five years she had been under observation.

Miss D. W., aged 16 (case 221), is of special interest because intrinsic causes must have been primarily responsible for the asthma although the clinical picture varied greatly from the above described syndrome. Her first attack coincided with the first menses at the age of thirteen. Since then, very acute and severe seizures occurred regularly every four weeks, always two to three days before the menses, subsiding within three days. During the past year, the attacks became more prolonged, gradually extending throughout the period of the menses, but varying in intensity according to the original pattern. They became so severe that the patient had to be admitted to the hospital 10 times during one year's period. On each occasion she was unconscious and in severe shock. Bronchoscopic aspirations were resorted to each time as a life-saving procedure. She always recovered promptly immediately after bronchial aspiration of large amounts of tenacious material. When, in September 1943, on a day of high ragweed count, during such an attack, the bronchoscopist was not available immediately on admission to the hospital, she died.

Physically, this patient presented the usual findings of marked emphysema and typical wheezing. There were no secondary changes such as bronchiectasis or pneumonitis. The electrocardiographic and roentgen-ray studies showed the heart and lungs to be normal except for the presence of emphysema. The eosinophile count ranged from 4 to 12 per cent. Skin testing revealed many moderately severe reactions to such extrinsic sources as foods, ragweeds and other inhalants. An attempt to hypo-sensitize her against some of these antigens, as well as diets and other eliminative procedures, did not produce any improvement whatsoever. Intracutaneous skin tests with anterior pituitary extract, theelin and progesteron produced flares, but no typical wheal. Injections of progesteron, which have been helpful in the treatment of similar cases with premenstrual asthma, gave no relief.

\* Addendum (May 17, 1947): Since August 1946 after being placed on a high caloric diet disregarding all positive foods, this patient has been practically free from asthma.

† Note: This is considered the most common mode of death in asthma.

## II. "INTRINSIC" CAUSES

Disregarding the symptom complex of intrinsic asthma, some have applied the term "intrinsic" when the asthma is believed to be exclusively or at least primarily due to causes arising from within the organism. In the following review of the various factors involved, it will become apparent that skin tests cannot be reliably employed for any of these intrinsic sources.

*Cold Sensitivity:* Most of the 323 patients displayed "sensitivity" to sudden changes in temperature, especially to cold. Exposure of their skin to cold temperature and, more frequently, inhalation of cold air, induced wheezing. In 21 cases, a history was obtained that ingestion of ice cold drinks had this effect. The literature discloses evidence that the production of histamine is stimulated by sudden application of cold. However, merely the physical stimulus of inhaled cold air may produce an attack, through irritation of the mucous membranes of the nose and bronchi. In none of our cases could the asthma be attributed exclusively to sensitivity to cold.

*Infection:* Bacterial infection may account for asthmatic seizures. On the other hand, the presence of pus and bacteria in the upper air passages or the sinuses does not necessarily indicate a primary infection. Cohen, Kline and Rudolph<sup>6</sup> observed that an allergic wheal may become indistinguishable from an inflammatory process after three hours. By the same token, a process manifesting all the earmarks of an infection in the sinuses, in the bronchial tree and even in the lungs, may be entirely due to allergy. In some of the cases of this series, allergic pneumonitis had been wrongly diagnosed "virus pneumonia" because no specific organism could be demonstrated as their excitant. True infections were present at some time or another in practically every case of our series. Asthmatic seizures induced in this manner usually improved with the aid of sulfonamides and penicillin. During the height of an acute infection, the skin reactivity to the common antigens often decreases in intensity or completely disappears.

*Endocrine Products:* Among the 148 women at the menstrual age and above, 47 gave a history of having had an aggravation of their symptoms before the menstrual period. This relatively high incidence corroborates a similar observation by Waldbott and Bailey<sup>7</sup> showing that 22 out of 125 patients with various allergic diseases exhibited this tendency. In the blood of these cases with premenstrual aggravation, a deficiency of estrogenic substance was demonstrated. In contrast with the observation of Zondek,<sup>8</sup> skin reactions with extracts of estrogenic substances were inconclusive upon intracutaneous testing.

*Psychogenic Factors:* In a disease as disabling and chronic as bronchial asthma, it is to be expected that many patients should develop certain mental complexes which tend to enhance their symptoms. The exaggerated attention given to the patient by their attendants, especially by parents, the many don'ts in the life of an asthmatic, the habitual use of certain drugs, the disruption of family life and marriage relationship as the result of attacks, finally

the fear of strangulation during an attack, are factors which may induce such complexes. There were, indeed, many patients in whom attacks could be precipitated by mental influences and controlled by the administration of placebos. This mode of origin was not found to be a dominant factor on careful analysis of each individual case.

*Other Possible Sources:* Among intrinsic agents, Urbach<sup>9</sup> discusses products resulting from parasites within the body, from digestion in the intestinal tract, certain physiological fluids such as insulin, colostrum and mother's milk. Most of these factors are of speculative interest only and it could not be ascertained in our cases whether or not they played a part.

### SUMMARY

1. Asthma has been classified as extrinsic and intrinsic according to whether causative agents are demonstrable which enter the system from without or arise within the organism. In addition, some have described a syndrome of intrinsic asthma characterized by such clinical features as age of onset at 40 or above, negative skin reactions, progressive course and intractability to therapy.

2. In order to determine whether or not such a syndrome exists and whether a distinction between extrinsic and intrinsic asthma should be made on the above basis, 323 individuals were selected from a total of 1,442 asthmatic patients. They had perennial, continuous wheezing and had been under observation sufficiently long to permit a proper evaluation of their conditions. Among those excluded were cases with asthmatic wheezing which might easily have been interpreted as allergic asthma of the "intrinsic" type.

3. In seven of the 323 patients, the disease progressed and five additional ones died. In none of these could the above described syndrome be identified. In three cases, no clues as to the origin of the attacks could be detected. In each one the pattern of the attacks appeared different and it is impossible to group them under the common heading of "intrinsic asthma."

4. Intrinsic causes were definitely responsible for attacks in a large number of the 323 patients. Among these the most important ones were sensitivity to cold temperature, to endocrine products (premenstrual aggravation!) and bacterial infections. Psychogenic factors, products of digestion, or such physiological fluids as insulin, liver extract, colostrum may or may not play a part. In no case were such intrinsic factors found to be the only causes to the exclusion of those termed extrinsic.

5. This evidence indicates that there is no justification for the diagnosis of intrinsic asthma as a symptom complex and that the concept of such a syndrome may lead to faulty diagnosis and to abandonment of treatment at a time when treatment is needed and may be most effective. The term "intrinsic asthma" based on the assumption that the disease is due to intrinsic causes is misleading since such causes are not present to the total exclusion of extrinsic causes.

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# DISSECTING ANEURYSM OF THE AORTA: A PRESENTATION OF FIFTEEN CASES AND A REVIEW OF THE RECENT LITERATURE \*

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DISSECTING aneurysm of the aorta was first described by Nicholls<sup>1</sup> in 1761. Laennec<sup>2</sup> in 1819 was the first to employ the term dissecting aneurysm and Swaine<sup>3</sup> in 1856 was the first to make a correct ante-mortem diagnosis. In 1863 Peacock<sup>4</sup> published his review of 80 cases and in 1933 Shennan<sup>5</sup> published his monograph of 300 cases, to which he added 17 of his own. Since then there have been many excellent descriptions of the various aspects of this disease, among them being the reports of Logue,<sup>6</sup> Schnitker and Bayer,<sup>7</sup> Peery,<sup>8</sup> Weiss,<sup>9</sup> and Sailer.<sup>10</sup>

Although dissecting aneurysm is not a common occurrence, it is of importance to the clinician because of the variable symptomatology that it may produce. Despite the fact that dissecting aneurysms have been recognized by pathologists for many years, it is only recently that clinicians have regarded it as more than a medical curiosity. In Shennan's<sup>5</sup> series of 317 cases, the diagnosis had been made in only seven. In 1942 Flaxman<sup>11</sup> reviewed 112 cases reported since 1933 and found that the correct ante-mortem diagnosis had been made in 25. Thus, of 431 reported cases, the diagnosis had been made in 32 (7.9 per cent).<sup>11</sup> Recently clinicians have become better acquainted with the symptomatology so that the diagnosis is made in 10 to 30 per cent of the cases. In this series the correct ante-mortem diagnosis was made in six of 15 cases (40 per cent).

The true incidence of dissecting aneurysm is not known but the autopsy incidence has been reported by various investigators as follows: .14 per cent (Flaxman<sup>11</sup>); .18 per cent (Peery<sup>8</sup>); .5 per cent (Weiss<sup>12</sup>); .7 per cent (Logue<sup>6</sup>); .22 per cent (Sailer<sup>10</sup>); and .4 per cent (Ritvo and Votta<sup>13</sup>). Mote and Carr<sup>14</sup> in a review of the statistics of the Coroner's Office in San Francisco found that dissecting aneurysm is the cause of 1.1 per cent of all cases of sudden death (after exclusion of death due to violence).

In this series 11 cases were in males and four were in females. This corresponds to the figures reported by McGeachy and Paullin<sup>15</sup> (74 per cent in males) and Glendy et al.<sup>16</sup> (11 of 13 were males).

The ages of our patients varied from 35 to 87 years. There were three cases between 31 and 40; one between 41 and 50; six cases between 51 and 60; three cases between 61 and 70; one case 75, and one case 87. It is interesting to note that in the cases that occurred in patients over 50 years of age, the ratio of males to females approaches 1:1 (6 males in 10 cases over 50); this was observed by Shennan.<sup>5</sup> Most cases of dissecting aneurysm

\* Received for publication October 1, 1946.

TABLE I

Case No.	Age	Sex	Color	Exertion Prior to Onset	Admitting Diagnosis	Final Diagnosis
1	38	Male	Colored	None	Dissecting aneurysm	Dissecting aneurysm of thoracic aorta
2	67	Male	Colored	None noted	Cerebro-vascular accident	Dissecting aneurysm of entire aorta
3	57	Female	White	None noted	Dissecting aneurysm of abdominal aorta	Incomplete rupture of the aorta
4	54	Male	White	None noted	Coronary occlusion	Dissecting aneurysm of entire aorta
5	75	Male	Colored	None noted	Pneumonia with poss. coronary occlusion	Dissecting aneurysm of thoracic aorta
6	40	Male	Colored	None noted	Dissecting aneurysm	Dissecting aneurysm of thoracic aorta
7	54	Male	Colored	None noted	Dissecting aneurysm	Dissecting aneurysm of arch of aorta
8	60	Female	Colored	None noted	Coronary occlusion	Dissecting aneurysm of abdominal and thoracic aorta
9	87	Female	White	None noted	Partial intestinal obstruction	Dissecting aneurysm of superior mesenteric artery
10	62	Male	White	None noted	Coronary occlusion	Dissecting aneurysm of thoracic aorta
11	46	Male	Colored	None noted	Lutic heart disease	Dissecting aneurysm of thoracic aorta
12	63	Male	White	During an argument	Coronary occlusion	Dissecting aneurysm of ascending aorta
13	60	Male	White	Driving to work	Dissecting aneurysm	Dissecting aneurysm of entire aorta with dissection of left common carotid artery
14	35	Male	White	At work at a desk	"La grippe"	Dissecting aneurysm of aorta
15	60	Female	White	At home doing housework	Dissecting aneurysm	Dissecting aneurysm

occur in patients between 40 and 70 years of age.<sup>17, 6, 18</sup> In Crowell's<sup>19</sup> series 80 per cent of the patients were over 40; 12 of Glendy's<sup>16</sup> 13 cases were in patients over 40, and 12 of our 15 were over 40. Schnitker,<sup>7</sup> however, in a review of 560 cases found 141 (25 per cent) cases in patients under 40 years of age. The youngest case was recorded by Frei<sup>20</sup> (14 months old) and the oldest was recorded by Shennan<sup>5</sup> as being nearly 100 years old.

The etiology of dissecting aneurysm is not clearly understood; but there are several factors which are believed to play a part. Certain of these are discussed below.

The relationship of trauma and exertion to the formation of a dissecting aneurysm is still disputed but most investigators<sup>7, 14, 21</sup> believe that it is purely coincidental. Weiss<sup>9</sup> stated that he believed that most of the cases reported following trauma are not instances of true dissecting aneurysm. Glendy et al.<sup>16</sup> found that 40 per cent of their cases occurred after mild exertion (two while stooping; one during the act of vomiting; one during intercourse; one while arguing a case in court). In a review of 127 cases McGeachy and Paullin<sup>15</sup> found a history of exertion at the time of onset in 33. In only two of our cases could we find any relation to exertion; one during an argument and the other incident to housework.

It was formerly believed<sup>17, 18, 6, 22</sup> that hypertension was of prime importance to the formation of a dissecting aneurysm, but recent investigators believe that hypertension is of secondary importance.<sup>7, 14</sup> The incidence of hypertension in cases of dissecting aneurysm has been recorded by various authors as follows: McGeachy and Paullin<sup>15</sup> (60 of 127 cases); Glendy, Castleman and White<sup>16</sup> (8 of 11 cases); Hamburger and Ferris<sup>23</sup> (1 of 6 cases); Shennan<sup>5</sup> (131 of 163 cases); Thomas and Garber<sup>18</sup> (107 of 151 cases). Ten of our 15 patients (67 per cent) had either a history of hypertension or elevated blood pressures on admission (table 3). Of the 560 cases reviewed by Schnitker<sup>7</sup> 80 per cent were found to be hypertensive, but in the 141 cases under the age of 40 only 50 per cent were hypertensive. Oppenheim<sup>24</sup> demonstrated that it takes a pressure of two to three thousand millimeters of mercury to rupture the aortae of fresh cadavers. In view of the above discussion it may be concluded that: (1) although hypertension is usually present, its absence does not exclude the possibility of a dissecting aneurysm; (2) it is doubtful if "increases of pressure alone could reach sufficient magnitude in human subjects to cause actual dissection of the aorta"<sup>10</sup>; (3) hypertension will be found in 70 to 80 per cent of the patients over 40 years of age, whereas only 50 per cent or fewer of patients under 40 years of age will be found to be hypertensive.<sup>7</sup>

Formerly syphilis was believed to be an important predisposing factor, but recent investigations show that it is of minor importance. Syphilis has been found in many cases of dissecting aneurysm, but this is believed to be coincidental. Thus, in a review of 141 cases Schnitker and Bayer<sup>7</sup> found only five cases of syphilis; Shennan<sup>5</sup> and Mote and Carr<sup>14</sup> found evidence of syphilis in 10 per cent and 18 per cent of their cases respectively; McGeachy and Paullin<sup>15</sup> found six cases of syphilis in a review of 127 cases of dissecting aneurysm, and in two of our 15 cases (table 4) there was either serological or pathological evidence of syphilis. In case 5 there was a luetic saccular aneurysm and luetic aortitis beyond the intimal tear which were not involved in the dissection. In case 11 the dissection progressed



through the area of syphilitic aortitis. Weiss<sup>9</sup> and Sailer<sup>10</sup> point out that in syphilis the pathological process tends to fuse the various layers of the aorta thereby hindering dissection. Weiss<sup>9</sup> also presents a case in which the dissecting aneurysm extended up to, but did not involve the syphilitic area.

In the cases occurring in patients under the age of 40 there seems to be a distinct relationship between pregnancy and congenital anomalies of the aorta, and dissecting aneurysms. Schnitker and Bayer,<sup>7</sup> in their excellent review of this subject, found 141 cases out of a total of 560 (25 per cent) to have occurred in patients under 40 years of age. Of this group 49 (approximately 35 per cent) were in females and 24 (49 per cent) of these were pregnant. In only two of these did dissection occur in association with labor (two were post-partum and 20 were ante-partum) so the dissection cannot be attributed to the strain and blood pressure changes occurring during labor. McGeachy and Paullin<sup>15</sup> report 26 cases in females, six of whom were pregnant. Kinney, Sylvester and Levine<sup>25</sup> have recently reported a case of coarctation and acute dissection of the aorta in a pregnant patient which was diagnosed ante-mortem. Whether a true cause and effect relationship exists between pregnancy and dissecting aneurysm is not known, but it may be due to the hormonal changes which occur in pregnancy which may, in some way, weaken the aortic wall so that it is more susceptible to dissection.

Another predisposing factor is the presence of a congenital anomaly of the aorta, especially coarctation. Hamilton and Abbott,<sup>26</sup> in a review of 200 cases of coarctation of the aorta, found that 33 (16.5 per cent) of these died of a dissecting aneurysm. Schnitker<sup>7</sup> found that 45 of his 141 cases in patients under 40 years of age had either a true coarctation or distinct narrowing of the aorta. The case reported by Kinney, Sylvester and Levine<sup>25</sup> had a true coarctation of the aorta. The explanation of the occurrence of dissecting aneurysms in coarctation of the aorta is that in coarctation there is a primary deficiency of the media with a resultant weakened wall so that dissection may occur more readily than in a normal aorta. None of our 15 patients were pregnant and in no case was there any evidence of coarctation or of other congenital anomalies of the aorta.

Probably the most important factor in the formation of dissecting aneurysm is disease or weakening of the vessel,<sup>14, 15, 10</sup> especially of the medial coat. The nature of this deficiency or disease is not definitely known. Some observers<sup>27, 28</sup> believe it is the "medionecrosis aortae idiopathica cystica" as described by Erdheim. Schattenberg and Ziskind<sup>29</sup> present two cases of dissecting aneurysm and in both the medionecrosis as described by Erdheim was present. Glendy, Castleman, and White<sup>10</sup> found it in six of their 13 cases. We were unable to find it in any of our 15 cases and Rottino<sup>30</sup> was unable to find it in any of his 12 cases. Holland and Bayley<sup>28</sup> found 27 cases of medionecrosis aortae idiopathica cystica reported in the

literature, all of whom died of the effects of a dissecting aneurysm. Sailer<sup>10</sup> and Rottino<sup>30</sup> have reviewed the medial changes which occur in dissecting aneurysm and both have described several different types of degenerative changes which occur in the media and for a description of these changes the reader is referred to the original articles. From the above discussion it can be concluded that medial change, the nature of which may be different in various cases, is of primary importance to the formation of a dissecting aneurysm. Whether the medial changes will be found to be similar to those described by Erdheim or of other nature is unknown, but it may be that if diligent studies of various sections of all aortae are carried out definite medial changes will be found in a great number of cases.

Atherosclerosis has been cited as playing a rôle in the formation of a dissecting aneurysm, but it by itself cannot be the sole cause for several reasons: first, atherosclerosis is least common in the ascending portion of the aorta and it is in this area that the great majority of intimal tears are located; second, the intimal tear usually occurs in the tissue between two atherosclerotic plaques and rarely through one. Shennan<sup>5</sup> found that in only six of 218 cases did the dissection begin at the base of an atheromatous ulcer.

It may be concluded that no single cause can be demonstrated as consistently producing the changes leading to a dissecting aneurysm.<sup>10</sup> Medial disease, the nature of which varies, and hypertension, with the systolic stretching and diastolic recoil seem to be the most important factors involved.

The pathogenesis of dissecting aneurysm although not definitely established, is believed to be as follows: as a result of the medial disease there is a rupture of the vasa vasorum with the formation of a medial hematoma, which splits the wall. This eventually ruptures through the intima (usual course) producing a rent in the intima through which the blood can force its way, thereby extending the dissection. The path of the dissection will vary with the location and extent of the medial lesion.<sup>17, 6, 14, 31, 10</sup> There are several cases on record in which no intimal tear could be demonstrated<sup>6, 32, 23</sup> and in this series of 15 there was one case (no. 8) in which no intimal tear could be found.

Peery<sup>33</sup> has recently reported a series of cases in which there are tears through the intima without true dissection. These he has labelled "incomplete rupture of the aorta" and believes that this may be a stage of dissecting aneurysm. We had one such case in our series (no. 3).

The intimal tear is usually located in the first few centimeters of the ascending aorta, but may occur anywhere. There is usually only one tear, but they may be multiple. The tear is usually elliptical or longitudinal and varies from 1 to 10 centimeters in length. The incidence of tears located in the ascending aorta, as given by various authors, is as follows: Schnitker and Bayer<sup>7</sup> (58 of 64 cases); Mote and Carr<sup>14</sup> (42 of 56 cases); McGeachy and Paullin<sup>15</sup> (42 of 79 cases); and Frei<sup>20</sup> (153 of 275 cases). McGeachy

TABLE II

Case No.	Location, Length and Direction of Tear	Extent of Dissection	Cause of Death	Degree of Atheromatosis	Other Findings
1	4 cm. below the arch of the aorta	Dissected down to the level of the diaphragm	Pneumonia	Moderate	
2	1 cm. elliptical tear $1\frac{1}{2}$ cm. above the aortic valve. 2nd tear just above opening of right coronary artery	Down to the bifurcation of the aorta	Hemopericardium. Rupture through adventitia 8 cm. above aortic valve. 300 c.c. of blood in pericardial cavity	Severe	Extensive atheromatous degeneration of aorta
3	Numerous tears through the intima extending into the media	No true dissection	Coronary artery disease	Severe	Extensive atheromatous degeneration of aorta
4	$1\frac{1}{2}$ cm. above the aortic valve. Angular	Down to the bifurcation of the aorta	Hemopericardium. 350 c.c. blood in pericardial sac	Severe	Hemorrhage into tissue between pulmonary artery and aorta and into the musculature of the left atrium extending down to A-V line and covering area where S-A node and A-V bundle are
5	6 cm. jagged tear at beginning of the ascending aorta	Up and around the arch to just above the aortic cusps, and also into the innominate	Hemopericardium. 350 c.c. blood in the pericardial cavity	Moderate	Also showed a saccular (luetic) aneurysm and luetic aortitis beyond the location of the tear. An old healed myocardial infarction
6	1st tear 2 cm. in length and just above opening of right coronary and the 2nd tear 4 cm. in length and $1\frac{1}{2}$ cm. above the first. These 2 communicated	To the level of the diaphragm	Hemopericardium. 250 c.c. blood in pericardial sac	Moderate	Tuberculosis of the left adrenal gland
7	1st tear a 1 cm. ragged vertical tear just above the left coronary ostia and the 2nd a 2 cm. transverse tear at the origin of the left subclavian	To the origin of the left subclavian artery	Cardiac dilatation and pulmonary edema	Moderate	Ruptured back into the lumen at the origin of the left subclavian artery

TABLE II—*Continued*

Case No.	Location, Length and Direction of Tear	Extent of Dissection	Cause of Death	Degree of Atheromatosis	Other Findings
8	No visible tears in the intima	From 7 cm. above to 7 cm. below the vertebral attachment of the diaphragm	Left pleural effusion. 500 c.c. bloody fluid in left pleural cavity	Marked	No tears in the intima or adventitia
9	Tear in the superior mesenteric artery, $2\frac{1}{2}$ cm. from its origin	Extended up the superior mesenteric artery for $5\frac{1}{2}$ cm.	Gangrene of the bowel with intestinal obstruction	Mod- erate	Thrombus occluded the artery and produced gangrene of the bowel
10	A rectangular tear $2 \times 3\frac{1}{2}$ cm. and $1\frac{1}{2}$ cm. above the aortic valve on the posterior aspect of the aorta	To the level of the diaphragm	Hemopericardium. 350 c.c. bloody fluid in the pericardial sac	?	
11	$1\frac{1}{2}$ cm. in length and $2\frac{1}{2}$ cm. above the aortic valve	To the level of the diaphragm	Hemopericardium. 350 c.c. bloody fluid in the pericardial sac	Severe	Tear through the adventitia on the anterior aspect of ascending aorta. Also luetic aortitis
12	A clean edged zig-zagged tear 1 cm. above aortic valve on the right lateral aspect of aorta	Extended down over the atria, beneath the epicardium and up along the aorta to where it broke through the adventitia	Hemopericardium. 350 c.c. bloody fluid in the pericardial sac	Slight	
13	Transverse tear $1\frac{1}{2}$ cm. in length, 2 cm. above the aortic valve	Extended down to a point 1 cm. above the bifurcation where there was a 2nd small transverse tear. Dissection extended up left common carotid and almost completely occluded the lumen	Hemopericardium. 200 c.c. fresh and clotted blood	Severe	No tear in adventitia. Thrombosis of right common iliac artery
14	2 cm. transverse tear at sinus of Valsalva	Down to the iliac artery	Hemopericardium	Mod- erate	Old healed dissecting aneurysm, beginning at ductus arteriosus
15	Just above the renal artery	Down into the right common iliac	Retroperitoneal hemorrhage	Marked	

and Paullin<sup>15</sup> found multiple tears present in 12 per cent of their cases, whereas Shennan<sup>5</sup> found multiple tears present in 11 per cent. In our series the location of the tears was as follows: Ascending aorta—10; descending aorta—two. In one case there was no tear present; in another the tear was in the superior mesenteric artery and in case no. 3 there were multiple tears

throughout the aorta. In four of our cases (27 per cent) more than one tear was present. "The localization of the greatest number of intimal tears in the supra-avalvular portion of the aorta appears to be due to the relative immobilization of the vessel at this point, together with the marked physiologic strain and pressure acting on this area."<sup>34</sup> Shattenberg and Ziskind<sup>29</sup> believe the reason for this localization of intimal tears is that it is in this portion of the aorta that medial degeneration most frequently occurs. It is probable that both of these factors play a rôle.

Once the dissection has begun it usually spreads centrifugally although occasionally it goes centripetally.<sup>10</sup> The dissection is limited to the ascending and transverse portions of the aorta in 30 per cent of the cases,<sup>5, 15, 16</sup> and extends to the abdominal aorta in 35 per cent. In about 15 per cent of the cases one will find a double-barreled aorta. In our series the dissection extended to the bifurcation of the aorta in four; to the level of the diaphragm in four; and to the arch of the aorta in three. In one case there was no true dissection (case no. 3); in another the dissection extended from 7 centimeters above, to 7 centimeters below the diaphragm (case no. 8); in one case the dissection involved the superior mesenteric artery (case no. 9); in one case there was a double-barreled aorta (case no. 14).

The dissection may take one of three courses: (1) progress and involve the entire aorta, and then rupture back into the lumen; (2) progress a variable distance and then cease (rare); (3) rupture through the adventitia into the pericardial, pleural, or abdominal cavities. This latter event is the most common result and occurs in 80 to 90 per cent of the cases and results in sudden death.<sup>17</sup> The incidence of external rupture is as follows: Frei,<sup>20</sup> 189 of 275 cases (73 per cent intrapericardially); McGeachy and Paullin,<sup>15</sup> 69 cases (74 per cent intrapericardially); Crowell,<sup>19</sup> 86 per cent of his cases; and Glendy,<sup>16</sup> 10 of 13 cases (31 per cent intrapericardially). Schnitker and Bayer<sup>7</sup> found rupture into the pericardium present in 78 per cent of their cases and in our series, rupture into the pericardium with cardiac tamponade was the cause of death in 67 per cent. Other sites of external rupture are the pleural cavities (more often the left)<sup>9, 15</sup>; mediastinum,<sup>16</sup> and abdominal cavities. Ten to 20 per cent of the patients will recover from the first acute attack, but half of these will develop a second dissecting aneurysm which may result in their death; the remainder, however, will recover and die of some other disease or accident. There are cases of healed dissecting aneurysm<sup>5, 35, 36</sup> on record in which the aneurysmal cavity became endothelialized and in some atherosclerosis developed.<sup>35</sup> Even if these patients recover from the dissecting aneurysm, many of them will die of congestive heart failure. Only one of our cases (case no. 14) had a healed dissecting aneurysm with endothelialization of the aneurysmal sac, but two and one half years later he had a second dissecting aneurysm which caused his death.

The diagnosis of dissecting aneurysm is dependent upon clinical awareness and acquaintance with the symptomatology and physical findings in

association with the location and direction of the dissection and the vessels affected. The symptoms most often found are:

*Pain:* This is the most striking symptom produced.<sup>17, 6, 14, 31</sup> It is usually sudden in onset, very excruciating, and often radiates to the back between the scapulae and into the neck. In some cases the pain radiates down the back and into the legs. The pain rarely radiates to the arms. The pain is usually precordial but may be substernal, epigastric, interscapular, or lumbar.<sup>15, 16</sup> In some the pain may begin in the legs. The pain is usually not relieved by ordinary doses of morphine. In our series of cases the location and radiation of the pain was as follows: In 10 cases the pain was above the diaphragm and in five it was below the diaphragm. In the cases in which the pain was above the diaphragm there were three cases in which it was substernal without radiation; two cases of substernal pain which radiated to back and epigastrium; two cases in which the pain was in the left lower

TABLE III

Case No.	Character of Pain	Dyspnea	Paralysis of Legs	Blood Pressure	Aortic Diastolic Murmur
1	Recurrent attacks nausea for 3 days. Prior to admission severe pain in back and epigastrium which persisted	None	Not present. Hyperactive reflexes on the right	Hypertensive for several years, 230/130 on admission, 230/140 on day after admission, 230/135 on 2nd day, 200/100 on 3rd day	None noted
2	Severe substernal pain and unconsciousness until death	Mild	Patient unconscious	No history of hypertension. B.P. 132/86 on admission. No other notations	None noted
3	Severe "indescribable" intermittent epigastric pain for the past month, which radiated through to the back	No note	Not present	Hypertensive for past 5 years. B.P. 220/140 on admission. No other notations	None noted
4	Sudden onset of severe substernal tightness which lasted 5 minutes and was followed by collapse	No note	Not present	For past 1-2 years. Averaging 170/120. B.P. on admission 50/20, rose to 106/60; 140/110 (R.A.) and 120/100 (L.A.) next day	None noted
5	For 2 days prior to admission mild stabbing pains in his left lower chest which radiated to the right	None	Not present	Known hypertensive for 5 months. 180/120 on admission. Fell to 110/70 on the second day, and then gradually rose to 120/80 by the 5th day	None noted

TABLE III—Continued

Case No.	Character of Pain	Dyspnea	Paralysis of Legs	Blood Pressure	Aortic Diastolic Murmur
6	Sudden onset of severe stabbing substernal pain which radiated to the back and epigastrium	Moderate	Not present	No history of hypertension. B.P. 215/110, rose to 270/140 2 hours later, then fell to 240/130 1½ hours before death	Loud aortic diastolic murmur, transmitted down left sternal border
7	Sudden severe pain in left lower chest	Moderate	Not present	No history of hypertension. 60/? on admission, 65/50 next day	None noted
8	Severe knife-like pain in R.L.Q. which radiated to back and left flank	Moderate	Not present	No history of hypertension. 113/84 on admission. 92/60 2nd day; 178/110 5th day; 120/90 14th day; 142/104 16th day; 114/80 20th day	No diastolic murmur noted. Loud systolic murmur at aortic area
9	Slight epigastric pain with nausea and vomiting for 3 weeks	None	Developed a right hemiplegia with hyperactive reflexes. Cleared up on 2nd day	No history of hypertension. 118/75 on admission. 120/65 next day	None noted
10	Sudden onset of substernal pain which radiated to epigastrium	Moderate	Developed a right hemiplegia with hyperactive reflexes 12 hours after admission	Known hypertensive for 3 yrs. (195/120). 150/120 on admission	None noted
11	Sudden onset of dyspnea and mild pains in region of heart. Went into shock, responded but died next day	Marked	Not present. Reflexes hyperactive	No history of hypertension. 180/90, both arms on admission. Dropped to 90/60 on 1/1/39 and rose to 115/70 on 1/2/39	Loud aortic diastolic murmur
12	Constricting pain in the suprasternal notch relieved by M.S. 7 hrs. later had sudden onset of severe nausea and vomiting, with mild epigastric pain. Relieved by M.S. Developed right hemiplegia 22 hrs. later and died in 1 hour	Marked	Hyperactive on right after developed hemiplegia	Hypotensive all of life. 75/56 when first seen, without any subsequent change	None noted
13	Sudden onset of severe pain in his throat. This was later replaced by substernal soreness and mild epigastric distress	Marked	No	No history of hypertension, 70/50 on admission. Rose to 130/70 that night; 145/90 next morning; 130/88 just prior to death	Faint aortic diastolic murmur at left sternal border

TABLE III—*Continued*

Case No.	Character of Pain	Dyspnea	Paralysis of Legs	Blood Pressure	Aortic Diastolic Murmur
14	Sudden onset of severe substernal pain which persisted for 2 days. Continued to work. No pain for past 4 days but has had a "cold." Had been in hospital 2½ years previously with sudden onset of severe lumbar back pain. No cause found. Cleared with symptomatic treatment	No	No	B.P. 155/100–185/120 for past 2½ years; 200/115 on admission. No subsequent notations	High pitched aortic diastolic murmur
15	Sudden onset of severe abdominal pain which radiated down both legs and out to the right axilla. Very thirsty and dizzy. Pain persisted and vomited (no blood)	No	No	B.P. 180/90 to 230/130 for past 12 years. 96/86 on admission. Dropped to 84/80, 2 hours later	No notation of any murmurs

chest, and in one of these it radiated across to the right; one case of precordial pain without radiation; in one the pain originated in the suprasternal notch and radiated to the epigastrium and in the other the pain began in the throat and later was replaced by a substernal pain. In the five cases in which the pain began beneath the diaphragm it was epigastric on three occasions. In one there was no radiation; in the second the pain radiated to the legs and right axilla; and in the third it radiated through to the back. In one case the pain began in the back and radiated around to the epigastrium and in the other case the pain began in the right lower quadrant and radiated to the back and flank. In no case was there any pain in either arm. The pain was described as being choking, constricting, knife-like, stabbing or crampy. In all cases the pain was intense. There have been cases reported in which there was no pain present.<sup>6, 24, 48</sup>

*Dyspnea:* This is frequently observed, but is believed to be secondary to the pain. In some cases, however, the dyspnea will be caused by a hemothorax resulting from leakage from the dissecting aneurysm.<sup>37</sup> McGeachy and Paullin<sup>15</sup> found that 30 of 127 patients were dyspneic and Glendy<sup>16</sup> found dyspnea in eight of their nine cases. In our series there were five patients who were not dyspneic; three with marked dyspnea; three with moderate dyspnea and one with mild dyspnea; in two cases there was no notation as to dyspnea.

*Syncope:* This has been noted by some authors,<sup>23</sup> and was observed in one of our cases (case no. 4).



*Hypertension:* The rôle of hypertension has been discussed earlier but we would like to point out that although some patients with dissecting aneurysm are in shock when first seen<sup>17, 7, 14, 23</sup> one of the most common findings is an elevated blood pressure, which does not fall.<sup>17, 16, 15, 7</sup> Ten of our 15 patients had either a history of or elevated blood pressure when first seen. In our series the blood pressure rose on four occasions, made no change in three and fell in four. In four cases no subsequent blood pressures were recorded.

A second important physical finding is the sudden appearance of an aortic diastolic murmur,<sup>17, 7, 38</sup> with or without other signs of aortic insufficiency. This is a frequent finding since most of the intimal tears occur in the ascending aorta and as a result of the dissection there may be a distortion of the aortic ring so that there will be improper closure of the aortic valves.<sup>7, 14</sup> Glendy et al.<sup>16</sup> observed a diastolic murmur at the base (with a systolic murmur) in four of 10 cases; McGeachy and Paullin<sup>15</sup> observed a basal diastolic murmur in two and a to and fro murmur in 14 of 32 cases; Schnitker<sup>7</sup> found an aortic diastolic murmur in 24 per cent of 141 cases. In our series an aortic diastolic murmur was noted in four of 14 cases (29 per cent).

TABLE IV

Case No.	S.T.S.	X-ray Findings	Hbg.	R.B.C.	W.B.C.	Polys	Hematuria	Electrocardiogram
1	None	Enlarged heart. No mention of an enlarged aorta	60%	3,350,000	12,000	72%	No	None taken
2	Negative	None taken	72%	3,850,000	9,800	78%	No urine report	None taken
3	None	None taken	81%	4,410,000	13,800	81%	No	None taken
4	None	None taken	75%	3,900,000	22,700	88%	No	Complete auricular ventricular dissociation
5	Positive	Saccular aneurysm of the arch of the aorta	72%	3,840,000	11,600	72%	No	None taken
6	None	Moderate degree of dilatation of the aorta. Heart at the upper limits of normal in size	88%	4,500,000	14,900	93%	No	None taken
7	Negative	Widening of the mediastinal shadow on the right. Enlarged heart	115%	5,810,000	21,400	81%	No	Deep depressed ST <sub>2</sub> and ST <sub>3</sub> . Ventricular extrasystoles. T-waves up-right

TABLE IV—*Continued*

Case No.	S.T.S.	X-ray Findings	Hbg.	R.B.C.	W.B.C.	Polys	Hematuria	Electrocardiogram
8	Negative	Marked enlargement of the heart to the right and left	65% (11/21) 53% (12/5)	3,690,000 3,030,000	15,700 10,200	89% (11/21) 75% (12/5)	No	Slurred QRS - Lead III, inverted T <sub>3</sub> . No other changes
9	None	No chest x-ray. Flat plate of abdomen showed dilated loop of bowel representing partial intestinal obstruction	90%	4,830,000	6,800	85%	No	None taken
10	None	None taken	None	None	26,000	83%	Few RBC in urine	All T-waves upright. Depressed ST <sub>2</sub> and ST <sub>3</sub> . Elevated ST <sub>4</sub>
11	Positive	None taken	94%	4,810,000	15,250	88%	Occ. RBC in urine	None taken
12	None	None taken	None	None	15,200	77%	No	None taken
13	None	None taken	85%	4,400,000	14,800	93%	No	None taken
14	None	None taken	90%	4,500,000	7,100	72%	No	None taken
15	None	None taken	48%	2,610,000	16,000	87%	Occ. RBC	None taken

One may also find evidence of an enlarged heart (if there has been pre-existing hypertension) <sup>6, 13</sup> and an increased area of supracardiac dullness, <sup>6, 13</sup> if the dissection involves the first portion of the aorta. If there has been bleeding into the pleural cavities, one will find the signs of a pleural effusion. <sup>37</sup> This is most commonly found on the left side.

A friction rub <sup>7</sup> is usually not found although there have been cases reported in which it was present. <sup>17</sup> Levine states that he often uses the absence of this finding to differentiate a dissecting aneurysm from a myocardial infarction. A friction rub was not noted in any of our cases.

Other signs and symptoms will vary, depending upon the vessels involved. Dissection of the following arteries will produce the symptoms noted:

Carotid artery: Hemiplegia; vertigo; syncope.

Renal artery <sup>39, 40</sup>: Pain in flank; hematuria; anuria; uremia.

Mesenteric artery <sup>6</sup>: Abdominal pain; diarrhea (with or without blood); signs of intestinal obstruction.

External iliac arteries <sup>6</sup>: Numbness, weakness, coldness and discoloration of legs.

Lumbar arteries: Bizarre neurological signs such as loss of reflexes, transient paralysis and paresthesias. <sup>6, 42, 41</sup> The frequent occurrence of

neurological signs results from obstruction of various lumbar and intercostal arteries with resultant ischemia of the spinal cord.

**Subclavian artery:** Symptoms similar to those present in the scalenous syndrome.

The laboratory findings of significance are:

*Leukocytosis*<sup>17, 18, 6, 7, 16</sup>: An increase in the leukocytes is usually present although some cases have normal counts. Thomas and Garber<sup>18</sup> found a leukocytosis in 45 of 48 cases and Logue<sup>6</sup> in eight of 10 cases. Twelve of our 15 cases had a leukocytosis of 11,000 or more. The counts varied from 11,600 to 26,000 with an average of 16,200. The percentage of polymorphonuclears varied from 72 to 93 per cent with an average of 84 per cent.

*Progressive Anemia*<sup>17, 18, 7, 32</sup>: This occurs as a result of the bleeding into the aortic wall and is not found in cases of coronary occlusion, rupture of the aortic cusps, ruptured chordae tendineae, or in rupture of the aorta into the pulmonary artery. In only one of our cases was more than one count done and this showed a 12 per cent decrease in the hemoglobin content.

*Hematuria*<sup>39, 40</sup> may occur if the renal vessels are involved.

*Positive Serological Test for Syphilis:* This will confuse the picture more than it aids, especially if the dissection produces aortic insufficiency. Two of our 15 cases had positive serological tests and both of these had evidence of cardiovascular syphilis at necropsy.

Roentgenological examination of the chest may or may not aid in the diagnosis of dissecting aneurysms.<sup>17, 6, 38, 43</sup> Wood et al.,<sup>43</sup> in an excellent review of the roentgenographic features of dissecting aneurysm, state that the common findings are as follows:

(1) A deformity of the supracardiac shadow. Frequently an arcuate excrescence extends outward from some point in the aortic arch. This shadow may or may not pulsate.

(2) The shadow alteration of the supracardiac shadow in successive films produced by an extension of the dissection is probably the most pathognomonic roentgenological sign.

(3) Displacement of the esophagus and trachea may occur.

(4) Often enlargement of the heart may be present.

(5) Frequently one will find evidence of fluid in the pleural cavities, especially the left.

Laminagraphic studies are of value in localizing the portion of the aorta involved,<sup>44</sup> but none of the roentgenological findings are pathognomonic. McGeachy and Paullin,<sup>15</sup> in a review of 22 roentgenograms in cases of dissecting aneurysm, found an increased aortic shadow in 16; cardiac hypertrophy in nine and pleural effusion in eight. All six of Gouley and Anderson's<sup>38</sup> cases had roentgenographic evidence of a dilated aortic arch. Chest roentgenograms were taken in five of our cases; an enlarged heart was noted in three cases; one had a saccular aneurysm; one had a moderate degree of

dilatation of the aorta; and one showed a widening of the mediastinal shadow on the right.

Electrocardiography will show no distinct or diagnostic pattern in dissecting aneurysm but is of great importance in excluding coronary occlusion.<sup>17, 18, 6, 7</sup> There have been cases reported in which the electrocardiogram showed changes similar to those found in coronary occlusion.<sup>45, 12, 23, 12</sup> Weiss presents a case in which the dissecting aneurysm compressed the mouth of the left coronary artery, producing a myocardial infarction of the left ventricle which was shown by the electrocardiogram. Hamburger and Ferris<sup>23</sup> present a case with progressive elevation of the S-T segment and inversion of the T-waves in Leads II and III with an increase in the depth of Q<sub>3</sub>. At necropsy, ecchymosis was found about the right coronary artery, one centimeter from its origin. White et al.<sup>46</sup> state that they "have never encountered a case of proved severe myocardial infarction with practically normal electrocardiograms through the first week of the acute illness." If one encounters a case of severe chest pain in a patient, who may or may not have hypertension, and who, after a week of illness, fails to show any significant changes in the electrocardiogram one should think twice before labelling this patient as a victim of coronary artery disease. In cases of pericardial effusion one may find elevated S-T segments and/or inverted T-waves.

Electrocardiograms were taken in four of our cases and showed the following: one showed complete auricular-ventricular dissociation (case no. 4). At necropsy, hemorrhage was found to extend into the tissue between the pulmonary artery and aorta and into the musculature of the left atrium, extending down to the A-V line and covering the area of the S-A node and A-V bundle. In the second case the S-T segments in Leads II and III were depressed and all T-waves upright. In the third case there was slurring of the QRS in Lead III with inversion of T<sub>3</sub>. In the fourth case there was depressed S-T segments in Leads II and III and elevation of S-T segment in Lead IV.

In a differential diagnosis one must rule out other causes of sudden severe pain such as coronary occlusion, pulmonary infarction, peripheral embolus and surgical conditions in the abdomen. Dissecting aneurysm differs from coronary occlusion<sup>31, 12</sup> in that the pain is usually more severe and has a wider radiation; syncope is often present; the blood pressure does not usually fall; there is no evidence of a pericardial friction rub. Sudden appearance of an aortic diastolic murmur is important; the electrocardiogram will show no diagnostic feature; and roentgenological examination may be helpful.

#### SUMMARY

1. Fifteen cases of dissecting aneurysm have been reported.
2. A review of the recent literature with a discussion of the symptoms, physical signs, etiology, pathogenesis, and pathological findings is presented.

3. The diagnosis rests on clinical perspicacity and evaluation of the presenting factors.

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## PSYCHOGENIC RHEUMATISM \*

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A COMMON problem in the practice of internal medicine is the patient who complains of aches and pains in the muscles and joints and chronic fatigue. Often there is slight fever but otherwise the physical examination and laboratory studies are negative. Attention is focused on this slight rise in temperature and the patient undergoes repeated and prolonged studies from the standpoint of obscure infection or endocrine dysfunction. Formerly such patients were often thought to be tuberculous; later rheumatic infection, with much attention to the heart, was suspected; nowadays chronic brucellosis is the most frequent diagnosis. In the course of the many physical and laboratory studies slight deviations from normal are detected and additional diagnoses are made which add to the patient's concern. She sees herself crippled by arthritis or heart disease and anticipates being a burden to her family. In addition to the many physical and physiotherapeutic measures that are used in treatment, rest and more rest is urged upon the patient, which perpetuates the invalidism and leads to greater restriction and a more impoverished life. This kind of a story continues, sometimes for years, often with prolonged periods of hospital observation and sanitarium stay.

These observations are based on a study of 40 patients encountered in a larger study of 200 patients with chronic fatigue, because so-called psychogenic rheumatism is only an aspect of the chronic fatigue problem. I do not care for the term psychogenic rheumatism because I am not interested in proving psychogenesis, and the term rheumatism is already surrounded with enough opprobrium without attaching to it the suspect word psychogenic. Psychosomatic does not mean to study the soma less; it only means to study the psyche more. Therefore I have been interested in studying these patients from an emotional as well as a physical standpoint to see if a relationship exists. The subject has received considerable attention in military medicine and in trying to apply the observations to civilian medicine I thought it advisable to use the term as a title although other designations, which will be mentioned, are preferable.

Of the 40 patient only five were men. All but four of the women were married. Physical findings of significance were uniformly absent. Halliday, whose observations on this subject are noteworthy, finds fibrositic nodules just as common in people who have no complaints as in those with so-called fibrositis, which is the diagnosis commonly applied to this syndrome in Great Britain. Sixteen patients had slight fever, always less than 100°,

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and in only two was there slight elevation of the sedimentation rate. Neither leukocytosis nor any other important abnormality of the blood count was found. Lowered metabolic readings were occasionally encountered and low normal fasting blood sugar levels, as well as somewhat flattened sugar tolerance curves, were rarely observed but it was always felt that these were secondary rather than causal features. The same findings were present after improvement.

Evidence for chronic brucellosis seemed positive in only one patient. Low back pain of a nagging character was a frequent association, and atypical neuralgias of the face, shoulder region, and leg, were frequently associated with the body aches and pains. "Sinus infection" was almost invariably held responsible for headache, "focal infection" for the atypical neuralgia, and slight pelvic abnormalities for pain in the back.

The referring diagnoses included arthritis, fibrositis, muscular and non-articular rheumatism; tuberculosis, rheumatic fever, and brucellosis; endocrine dysfunction, especially asthenia of thyroid and adrenal origin, adrenal cortical insufficiency being a frequent diagnosis. Hypoglycemia, low blood pressure, anemia and avitaminosis occurred again and again in almost every history. Neurocirculatory asthenia and constitutional inadequacy were frequent diagnoses. Colitis, autointoxication, and autonomic imbalance were often mentioned. If the patient was anywhere near middle-age, menopause was invariably held responsible, both in women and men, so that injections of estrogenic substance or testosterone were almost as frequent as injections of vitamin B<sub>1</sub>.

Psychosomatic study, meaning the simultaneous application of physiological and psychological technics, proved the presence of psychopathology rather than tissue pathology. Hysteria was encountered in 16 patients, anxiety states in 11, hypochondriasis in two, and two suffered from psychotic depressions. The latter two were helped by electric shock. In nine patients I was unable to make a precise psychiatric diagnosis other than an underlying neurotic character. The one patient with rather definite evidence of chronic brucellosis, as indicated by suggestive history and high titers in the agglutination reaction, in addition to positive skin tests, had a pronounced personality disturbance which antedated the onset of the illness.

Psychological symptoms most frequently encountered were poor sleep and poor sexual adjustment, and a marital problem was the most frequent underlying problem. Significant emotional conflicts were found which were apparently responsible for the fatigue, but the special feature associated with muscular aches and pains was the presence of chronic resentment of which the patient was usually totally unaware.

### DIAGNOSIS

Psychosomatic diagnosis means more than diagnosis by exclusion. It means the utilization of physiological and psychological technics simultane-



ously in preparation for comprehensive medical care. We do not have to change our history form—we only have to change our point of view. Diagnosis by exclusion is dangerous in these cases and leads to greater invalidism. The physician becomes a pathogenic agent in perpetuating the illness by his well meaning but mistaken and never-ending efforts to find a "physical cause." The problem is not so complicated that we cannot complete our physical studies with dispatch and at the same time make psychological observations.

Therefore, one may follow the standard form of history taking but in accordance with what has already been said more attention will be paid to the behavior of the patient and to the actual words that he uses in describing his complaints as well as the asides and apparent irrelevancies that so often give important clues to the emotional factor. Other fundamental considerations are to give the patient time, allowing him to talk with as few interruptions as possible; avoiding extensive note-taking so that the patient may feel that you are more interested in him as a person than in the setting down of the history; showing interest and sympathy for what the patient sometimes regards as trivial or silly; paying more attention to the chronological development of the life history with emphasis on the various factors in the childhood period that may have influenced the development of the personality; giving special attention to puberty and adolescence with the frequent emotional problems of that period; paying attention to the epochs and crucial periods in life when psychosomatic disturbances are apt to arise; and, particularly, obtaining a more complete picture of the family background.

Just as we try to establish a kind of Koch's postulate for an allergic problem, hay-fever for example,

- (1) heredity
- (2) seasonal history
- (3) skin tests
- (4) antibodies
- (5) induction of an attack with pollen
- (6) hyposensitization or avoidance of offending substance in controlling attacks,

so in the psychosomatic problems we try to establish,

- (1) the family history (heredity and pseudo-heredity)
- (2) evidence for a childhood neurosis
- (3) sensitivity to specific emotional factors (temporal relationship of present illness and emotionally disturbing event) especially at epochal or crucial life periods (puberty, marriage, childbirth, climacteric, etc.)
- (4) a specific personality structure (other evidence of neurosis or character disturbance)

- (5) demonstration of specific behavior on taking the history (artificial exposure to a conflict situation)
- (6) hyposensitization by psychotherapy or the avoidance of the provocative situation.

We will not be able to establish all of these postulates in every case. For example, evidence for a childhood neurosis will often be lacking—neither the patient nor his family can recall disturbed behavior or bodily dysfunction. But if we adhere to these criteria we can establish the diagnosis on positive data from an emotional standpoint at the same time that we are making negative observations from a physical standpoint.

If we listen as carefully to what people say as to the sounds that their hearts make, we will often find that they express their problem in symbolic language. Thus a middle-aged, frigid woman married to a rather immature man, whom she compared to his arrogant father, asserted "when pop sticks out of him it's war with me." Another patient whose ache was in her life situation—for years she had been a martyr to a sick and demanding mother—spoke of "being one big pain from head to toe." An hysterical woman who suspected that her fading charms would no longer hold her husband's affections spoke of her "feverish love" for him. Again and again we find these patients "burned-up", with resentment and "aching" to express their unappeased hostility.

*Psychopathology.* Nowadays lack of energy is apt to be explained by lack of vitamins; but, while these patients are sometimes too tired to eat and may not get an adequate diet, this is certainly not their primary problem. What we must interest ourselves in is not so much a lack of vitamins but the lack of emotional satisfaction in their lives. There must be some kind of a balance to the emotional life—too much expenditure on conflict with too little satisfaction coming in and the patient is headed for emotional bankruptcy.

In the same way instead of looking for focal infection we had better look for focal conflict and often we will find it in regard to a marital or parent-child problem. Emotional conflict, which uses up energy that is then no longer available for work or social purposes, is the commonest cause of chronic fatigue. The special feature of the patients with muscular aches and pains is the presence of smoldering resentment. Usually they are not aware or are only dimly aware of it, but when it is brought to the surface and their feelings somewhat relieved improvement takes place. As Sherrington expressed it, the best way to deal with tension of emotional origin is action, the next best way is by speech and the least effective is by thought, which means that if people have tension of emotional origin and can do something about it, punching someone they dislike, for example, or telling him off, they often relieve their tension, regardless of other consequences. But the person who says, "Oh, what is the use of fighting; after all, she is my mother, sister, daughter"—that person, who does not realize the amount of

aggravation in her day-to-day existence and certainly does not know how angry it makes her or what hostile feelings she is accumulating—that kind of a person is unable to relax and her rebellion takes the form of constant muscle tension. If we stop to think for a moment it is clear why this should be so. As Ellman et al. point out, the muscles serve as a means of defense and attack in the struggle for existence and thus internal tension is most easily relieved by muscular action. When the external expression of aggression in the form of muscular action is inhibited by repressing forces, then muscular tension may result which is felt by the individual as pain and limitation of movement and is often erroneously interpreted by the examining physician as fibrositis or muscular rheumatism. In Ellman et al.'s study of 50 civilian and military cases labelled as fibrositis, 35 suffered from common psychological disorders bearing on and of probable etiological significance for their complaint. Twenty-five of the 35 were classed as hysterical conditions, seven as anxiety states, and three as depressive states. More recently Boland and Corr found psychogenic rheumatism to be the most frequent cause of disability in 450 consecutive cases diagnosed as arthritis or allied organic conditions in an army general hospital. Approximately one third of the patients in the entire series were considered incapacitated because of psychic difficulty. The sedimentation rate was normal in all cases and in one third of the cases there was a history of invalidism or semi-invalidism from rheumatism in one or more members of the immediate family.

An outstanding characteristic in their patients with psychogenic backache was persistence of disability in spite of prolonged bed rest. They emphasize this feature of the disability in dramatic fashion when they cite the patient with advanced active rheumatoid spondylitis who was found pushing another with pure psychogenic backache to the post-exchange in a wheel-chair.

Halliday has been chiefly responsible for calling our attention to this important syndrome in civil medicine. Working as medical referee with the insured population of Scotland, he surveyed a series of 145 consecutive patients labelled "rheumatism" (including fibrositis, lumbago, sciatica and neuritis), and found that 57 of them (i.e., 39 per cent) were incapacitated because of psychoneurosis. Thirty-seven per cent of an additional similar series of 62 patients examined by the same author were regarded as being disabled because of psychoneurotic disturbances. The incidence of "psychoneurotic rheumatism," he says, rises still further—to 40–60 per cent—if only those patients are considered who have been on the sick list for two months or more.

Elsewhere the significance of organ language has been pointed out.<sup>10</sup> When the individual is unable to express his tension by word or deed, his body sometimes takes over the function of saying things for him that he cannot say with his mouth. Thus the individual who is unable to swallow, in the absence of organic disease, sometimes cannot swallow something in his life situation and in the same way the individual with muscular aches and

pains would often like to express his aggression against someone in particular but is prevented from doing so by the affection or respect for that person that is mingled with his hostility. Hence, persuading such patients to talk about focal conflict may provide an answer to the problem.

Another very satisfactory way to get people to discuss themselves in relation to their illness is to use a case illustration. Repeatedly this is effective when other methods of trying to make people see the relation between emotions and illness fail. If one can think of an apt case illustration, the patient can readily identify himself and, even where there are marked divergences, the patient will often see a partial application which will encourage him to talk about his personal life. Sometimes he will deny the application only to go on from that point to discuss emotional factors of importance which previously he was unable to think of.

I do not know the cause of the slight fever such cases often present but I do not look upon it as significant. Reimann's study of the problem of long-continued, low-grade fever concerned 16 women. In them he found a high incidence of neurosis. He concluded that a certain proportion of normal individuals have temperatures regulated at levels slightly higher than  $98.6^{\circ}$  and that temperature of these levels is often found in neurotic persons. Certainly it is a mistake to focus the attention of the patient on this slight fever as an indication of "an obscure infection" to which we must devote our attention "until the cause is found." Nor is it necessary to call it psychogenic. In other words, in regard to this whole problem I prefer to regard the physical and psychological aspects as but different phases of the disordered constitution, perhaps parallel manifestations of the same basic fault, existing together and related to one another. In other words, psychological forces and somatic manifestations may have their roots in the same unconscious processes which discharge partly on the level of psychic representation through thoughts and feelings and partly on the physiological level through the autonomic nervous system. We know, for example, that slight disturbances in temperature regulation occur throughout the menstrual cycle, especially in some women, and these patients seem to be especially sensitive in this regard. Moreover, as Flind and Barber point out in a study of this disorder among Royal Air Force Personnel, there seems to be a lowering of the threshold for the appreciation of bodily sensation in some cases of neurosis. This leads me to say a few words regarding "constitutional inadequacy" which I look upon as a very unfortunate term. Most of these patients are not constitutionally inadequate even though, as one stated, she was always "a tired and achy" person. As Dunbar has pointed out, we must distinguish between pseudo-heredity and pure heredity. The child who grows up with a chronically sick and tired mother is apt to identify herself unconsciously with her mother and, despite contrary conscious efforts, will often repeat the pattern of the mother's life. In other words, if we look to the environment, to the family group especially, for the origin of these psychosomatic disturbances, we will often find emotional con-

flicts, and by bringing the material to the surface, and dealing with it in a more realistic way we can sometimes help them to become useful citizens again, instead of labelling them constitutionally inadequate or burdening them with that other equally unsatisfactory term, neurocirculatory asthenia, which is usually just a name to cloak our ignorance of the life situation of the individual.

The same strictures apply to the various symptom diagnoses that are often made in the study of these patients and to which too much attention is paid, increasing the anxiety of the patient. Slight anemia, somewhat lowered blood pressure or basal metabolism, somewhat depressed fasting blood sugars or even flattened blood sugar curves, intimations of endocrine dysfunction as a result of more elaborate hormonal assays, only perpetuate the invalidism. In other words, the physician often becomes a pathogenic agent when he approaches these patients purely from an organic standpoint and stresses insignificant physical or physiological deviations.

Probably the most difficult problem at the present moment is the question of chronic brucellosis. We are warned again and again that we must not make a diagnosis of neurasthenia, which under such circumstances is a psychological term without psychic meaning, until we have ruled out the possibility of chronic brucellosis. It is unquestionably true that chronic brucellosis occurs and produces a clinical picture not unlike the one we are describing but in the first place we ought to be able to establish that diagnosis with some certainty and without too much delay and secondly we must not forget, as Harris points out, that the two disorders—brucellosis and specific forms of psychoneurosis—may coexist. In this connection I would like to say that the emotions often exploit an organic illness and thus it is that frequently in connection with an infectious disease or after operation, convalescence lingers and invalidism sets in. Repeatedly our patients tell us that "they haven't been the same since their child was born—they gave all their strength to the baby," or "they haven't been right since an operation," especially a pelvic operation. Or the illness began following a slight respiratory infection. The belief is widespread that the organic disease produced the neurosis, whereas the actual mechanism is that the organic process has broken down the individual's psychological defenses, regression occurs, and the individual's predisposition, determined by his personality structure, permits the neurosis to emerge.

A contrary aspect of the relation of organic disease to neurosis is the severe neurotic disorder, hypochondriasis, for example, in which the patient is obsessed with his neurotic symptoms and inattentive to some serious disorder. I have frequently observed that the patient who insists "that his illness is physical" is apt to be suffering from a disorder of emotional origin while the patient who is eager to blame it on the psyche often has an organic disease.

## TREATMENT

In approaching the patient from the standpoint of psychosomatic diagnosis one must realize that in dealing with the emotions one cannot separate treatment from diagnosis and that really as soon as one has made an initial contact with the patient the groundwork is being prepared for treatment. There can be no sharp division between the period of diagnosis and the period of beginning treatment.

I would urge that the physical aspects of the study be completed as quickly as possible. One of the great difficulties about the organic approach in medicine is that we can always think of another process—obscure infection, hormonal disturbance, metabolic or allergic disorder—that we must continue to investigate and hence it is that these patients go through repeated and prolonged periods of observation, each one adding to the difficulty by focusing attention on a part rather than on the whole. This applies especially to brucellosis which is a particularly vexatious problem at the moment because so many patients get skin tested that the tests themselves induce immune reactions resulting in low titre agglutination responses.

I would also urge, once we have satisfied ourselves that the slight temperature elevation is only an insignificant phase of the disorder, that instead of suggesting to these patients that they keep a record of their temperature we tell them to stop taking it. Sometimes the desire is so pronounced that they have to be told to throw their thermometer away.

Once we have excluded physical disease and done it expeditiously we can say to these patients that they have no evidence of organic disease, and often it is wise to add at this point, or a little later, that neither do they have evidence of mental disease because so often with lay misconceptions regarding emotional problems, to suggest that the disorder is emotional means to the patient that it is mental and that he may be in danger "of losing his mind."

I always ask the patient toward the end of the study, "what have you thought about the cause of your illness?" We will often be amazed at the extraordinary ideas that these patients have had, some of which they have themselves contributed from their reading or fantasies and some of which have been supplied by the many medical examinations and investigations that have been done. The first rationalizations of anxiety have to do with "chronic and crippling arthritis which is going to make a life-long invalid of me, and thus I will become a burden to my family." Often they are thinking about heart disease because of the suggestion of rheumatic infection and the attention that the physician pays to the heart; of an obscure infection; of "autointoxication" or "blood poisoning," or of syphilis or even of cancer. Because of their inability to concentrate or because their memory plays them tricks they have the fear of losing their mind and often associated with it suicidal thoughts which are very distressing. We can make no headway with these patients from a treatment standpoint until we have these first

layers of anxiety out on the surface. It is like the layers of an onion; as they are peeled off, new problems present themselves and these new problems will invariably be found within the family group. Marital incompatibility and sexual difficulties are almost always present but the patients often hesitate to discuss them because they regard them as personal problems unrelated to their illness.

When we say to these people that their aches and pains and fatigue are due to the fact that they are always in a state of tension, that they do not know how to relax, even at night, and that because their muscles are taut they are crying out in protest with aches and pains, it makes sense to them and provides a stepping stone for them to begin to talk about their emotional problems. To some people I may make the additional suggestion that, after all, emotional immaturity is the background of a psychosomatic disorder and that "growing pains" that occur later in life are apt to be more painful than when they occur early in life.

Chronic resentment—smoldering discontent—is the special emotional problem in these patients but it had better be approached indirectly. One must avoid the crude suggestion that they are angry at someone who is supposed to be near and dear to them or for whom they are supposed to have filial respect. That problem can be approached by gradually making the patient aware of the discontent and chronic aggravation in his life as we study his day-to-day existence and note how his tension increases finally to the point where symptoms appear.

In other words, we must let them see that they are suffering not from disease of body or mind but rather from a disorder of their feelings. Then they will often tell you how "burned up" they have been and of the really great amount of hostility that has been dammed up behind a surface complacency.

Instead of cautioning rest and more rest, which only permits these people to "stew in their own juices," I recommend "that they carry on in spite of symptoms" and this they will often be able to do once they have divorced their pain from the fear of arthritis, heart disease, cancer or what not. Once neurotic pain is divorced from a fear of organic disease, it is remarkable how rapidly it will disappear or diminish. At the same time I recommend that they do not talk about their illness to their friends but try to cultivate the atmosphere of health by telling people that they are well no matter how badly they feel. As soon as possible I try to get them away from injections of vitamins and hormones, from sedatives and even physiotherapy, or if some of these measures are continued I make it clear to them that they are being used in a supplementary capacity and that the cure lies in emotional re-education. Halliday has called attention to physiotherapy and fixation of symptoms in his insured patients and we see the same thing in private and hospital practice. It is of course sometimes necessary to make certain concessions to the previous organic miseducation that the patient has had. We cannot go too quickly in changing our approach from disease to disorder,

from the idea of doing something for the patient to having him do something for himself, from education along physical lines to the necessity for emotional growth. The essence of the psychotherapy, which should be a part of the equipment of every physician, is not to go faster than the patient is prepared to go, because as Lindemann has said, clumsy psychotherapy can be as dangerous to the social life as poor surgery is to the physical life.

In connection with physical medicine I think one more word ought to be said and that is the problem of belts, braces and supports. So often we find these patients wearing sacroiliac or abdominal supports when what they need is inner support. Instead of trying to bolster them up with a crutch what we ought to do is try to develop their inner, emotional security so that they won't have to lean on supports, or braces, or for that matter on their physician.

Just as in a consideration of somatic disease it is necessary to make a complete diagnosis before we can hope to apply scientific treatment, so in psychosomatic medicine it is equally necessary. Hence, just as in general medical teaching we have always emphasized etiologic, anatomic, and functional diagnosis, so in psychological medicine, as pointed out by Levine, it is necessary to make a clinical, dynamic, and genetic diagnosis before one can stand on safe ground in regard to psychotherapy.

The clinical diagnosis in psychosomatic medicine refers to the structural and physiological deviations as well as to the underlying or associated psychological disturbance. For example, in this syndrome we would like to know whether we are dealing with a mild personality disorder such as hysteria or a severe personality disorder such as hypochondriasis. From the standpoint of the physician-patient relationship it is important to know whether the symptoms are on the basis of conversion hysteria or a part of the clinical picture of depression in which the mood disturbance is overshadowed by the somatic complaints. When one deals with depression there is often the threat of suicide.

Dynamic diagnosis refers to the meaning and purpose of the symptoms in terms of behavior. Coupled with the genetic diagnosis, which is derived from the longitudinal survey of the individual life history, we are then in a position for comprehensive medical care.

Instead of calling this psychogenic rheumatism, fibrositis, or even muscular rheumatism, the most suitable diagnostic term, as Flind and Barber point out, is the psychiatric diagnosis applicable to each case because it is the psychopathology that is chiefly responsible for the syndrome and it is by means of psychotherapy that we can deal with these patients most effectively.

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# A STUDY OF MITRAL STENOSIS IN PATIENTS WHO SURVIVED THE AGE OF FIFTY \*

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FEW studies have been made of mitral stenosis in persons who have passed middle life, although many excellent papers have been published on the natural history and course of rheumatic heart disease in over-all age groups and in young people. In only a few of these writings has the material been so arranged that information pertaining to older patients is available. We have found no paper which confines itself to mitral stenosis as the only existing valvular lesion in patients of advanced age. Boas and Perla<sup>1</sup> discussed mitral stenosis after 50 but included combined valvular lesions. For a number of years, one of the authors (L. A. B.) has been interested in the characteristics of rheumatic valvular disease in the older patients. As a result, this study of isolated mitral stenosis in patients who survived the age of 50 has been made. Particular attention was paid to the history of rheumatic fever, age of occurrence, time intervals relative to the onset of symptoms, congestive failure, and death. The diagnostic findings, complications, and mode of death are other points which have been of interest.

## MATERIAL

The material used has been collected from patients whom we have studied during the past four years at this Hospital, plus patients seen in private practice. The vast majority of the patients seen by the Cardiac Service of this Hospital during these years were veterans of World War I, whose average age approached 50. The large amount of cardiac material seen in this relatively limited age group permitted us to assemble this series of cases. No patient was included who was not known to have survived the age of 50.

The clinical diagnosis was based on the typical diastolic murmur at the apex. No living case was included in which the character of the murmur was questionable. Two cases are included in which no such murmur was heard during life, but isolated mitral stenosis was demonstrated at autopsy. All but one of these patients were examined by one or more members of the Cardiac Section, and in this instance, the diagnosis was verified at post mortem. Since mitral stenosis in these older patients is frequently associated with disease of other valves, careful attention was always given to this

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point. All cases were eliminated in which there existed any such suggestion. On the basis of these criteria, we were able to select 106 cases from our files. All but two of these patients were males.

The frequency of mitral stenosis in patients beyond the age of 50 is not easily determined from the literature. Cohn and Lingg<sup>2</sup> found that only 16 per cent of the patients with rheumatic heart disease included in their series lived beyond the age of 45. Willius<sup>3</sup> indicates that only one of 124 patients with mitral disease lived past the age of 50. These data would indicate a lower incidence than the reports of other authors. Samways<sup>4</sup> found the average age at death in 196 patients to be 38, but 10 per cent lived beyond 60. Cabot<sup>5</sup> indicates that 30 per cent of his cases of mitral stenosis passed 50 years of age. Boas and Fineberg<sup>6</sup> studied the correlation of hypertension with mitral stenosis in 135 patients, 46 of whom were over 50. Levine and Fulton,<sup>7</sup> in a similar study of 762 patients, show 54 of the series to be over 50 years of age. In the series studied by Horns,<sup>8</sup> 91 of 144 cases were 45 or past. Stone and Feil<sup>9</sup> discuss 100 autopsied cases of mitral stenosis (46 per cent combined lesions), of whom 28 were past 50 years of age. Clawson<sup>10</sup> indicates indirectly in his statistical study of autopsy material that approximately one-third of those with mitral disease alone lived beyond 50. White and Bland<sup>11</sup> have drawn attention to the fact that mitral stenosis may occasionally exist in the very aged. The conclusion of Levine and Fulton<sup>7</sup> that approximately 20 per cent of those with mitral stenosis live beyond 50 seems justified. No conclusion can be gained from our material since it is made up of a relatively fixed age group.

### HISTORY OF RHEUMATIC FEVER

A definite history of rheumatic fever was elicited in 31 cases; a history of chorea was noted in one patient. Only definite, acute, multiple joint involvement and chorea were considered as manifestations of rheumatic fever. The less typical manifestations were so difficult to evaluate in these older patients that they were not included. In nine cases, the records contained no information relative to this point, therefore, a definite history of past rheumatic infection was established in 32 of those patients upon whom information was available. This is a considerably lower incidence than that usually reported: DeGraff and Lingg<sup>12</sup> obtained a history of rheumatic fever in 70 per cent of their cases, while Hedley<sup>13</sup> reported a positive rheumatic history in 66.2 per cent of 916 fatal cases of rheumatic heart disease. White<sup>14</sup> found that about 75 per cent of such patients have a positive rheumatic history. Levine<sup>15</sup> gives a somewhat lower figure of approximately 50 per cent. A history of rheumatic fever was present in 56.6 per cent of 100 autopsied cases of mitral stenosis studied by Stone and Feil.<sup>9</sup> The above statements were based on studies of clinical material, in which the average patient was much younger than those included in this study. Boas and Perla<sup>1</sup> found the incidence of positive rheumatic history to be nearly identi-

cal with our findings in a series of cases of similar age. It may also be pointed out that studies of aortic stenosis, which involves similar age groups, discloses a positive history of rheumatic fever in 30 to 50 per cent of the cases.<sup>16, 17, 18</sup>

It seems that the history of previous rheumatic fever can be established much less frequently among the older patients. In part, this may be due to faulty memory; however, it is our impression that a well-defined attack of rheumatic fever causes sufficient distress and prolonged morbidity so that it is rarely forgotten.

The initial rheumatic attack occurred before the age of 20 in 18 of the 31 patients; it occurred before the age of 10 in 7 and after 30 in 2, the oldest being 40 years. The average age at the initial attack was 18 years. Two acute episodes had occurred in seven patients. The average age at the time of the initial attack in these 32 patients was approximately 10 years greater than that reported for over-all age groups. Bland and Jones<sup>19</sup> found this average age to be eight years. Stroud et al.<sup>20</sup> were in essential agreement while Cohn and Lingg<sup>2</sup> state that the onset of the disease occurred before the age of 15 in 70 per cent of their series.

There is some difference of opinion expressed in the literature regarding the relationship of the later onset of the disease to the ultimate course. The papers of DeGraff and Lingg<sup>12</sup> and Davis and Weiss<sup>21</sup> are quite definite in the implication that the later the initial infection, the shorter the course of the subsequent heart disease. Cohn and Lingg<sup>2</sup> concluded that the later onset was favorable to a somewhat longer course. The data included in the discussion of auricular fibrillation by Stroud et al.<sup>22</sup> would indicate that on the average the duration of the disease was longer in persons in whom the initial infection occurred after the age of 20. DeGraff and Lingg<sup>12</sup> found the mean duration of the disease to be 15 years with 75 per cent under 23 years. Davis and Weiss<sup>21</sup> indicate that only one-fourth of the cases studied by them lived over 25 years and state that the duration was 30 per cent longer if the initial infection occurred before the age of 10 years. Cohn and Lingg<sup>2</sup> found the average duration to be slightly under 13 years.

The duration of the disease in this group of patients was unusually long. For those patients who are dead, the average duration was 37.5 years, while the disease had existed in those still living an average of 32.9 years. It is apparent that the later age of initial infection (18 years) did not prevent the disease running a long course. The advanced age of these patients is accounted for the most part by a long course of the disease rather than by a late onset.

Pathological studies indicate that most persons who live past middle age with rheumatic heart disease have had the affliction for a long time, since evidence of rheumatic activity is rarely found at autopsy. Console<sup>23</sup> in his very excellent study on this point noted evidence of activity was rare in patients dying after 40 and only three of 24 patients dying after 50 had such evidence. de la Chapelle et al.<sup>24</sup> also indicate that evidence of rheumatic

activity is comparatively infrequent after the age of 40. Davis and Weiss<sup>21</sup> point out that the longer the duration of the disease, the less frequently is evidence of rheumatic activity found. It seems reasonable to conclude that most of those patients who reach advanced age with mitral stenosis have lived with the condition for many years and that the rheumatic process has become inactive. The uniform results of pathological studies sustain this view. If a late onset of rheumatic infection were responsible for the advanced age, then it would be expected that evidence of activity would be found much more frequently in autopsy material.

It is also of interest to speculate as to the significance of the frequent absence of a history of rheumatic fever among these patients. While faulty memory may be a factor, it does not seem that it can be held responsible for more than a small fraction of the discrepancy. It has been our impression that the majority of these persons never did have typical rheumatic fever, but that they did have atypical infection. This did not result in definite joint involvement or chorea, but during the course of the infection, the heart was involved. Though such a situation has for a long time been considered probable, the recent work of Rantz et al.<sup>25</sup> furnished objective support to this conception. They have noted conclusive electrocardiographic signs typical of rheumatic fever in patients following streptococcal infections without any evidence of joint involvement. They also noted similar changes preceding the onset of joint symptoms. If it is assumed that such a large proportion of the mitral stenosis cases in this age group have sustained their cardiac damage through this atypical type of infection, it is also possible that the advanced age to which they live is dependent, in some manner, on the characteristics of the initial infection. This might be explained on the basis that the cardiac involvement under such circumstances is comparatively mild, and for the most part, is confined to the endocardium insofar as permanent irreversible changes are concerned. Under such circumstances, valvular deformity could develop over a period of time without there having occurred any significant myocardial damage. The development of definite stenosis as a result of slow fibrosis might take a period of several years. Heart failure would not be expected to occur in early life under these circumstances. It has been established that the deaths from rheumatic heart disease follow a bimodal curve, those occurring before 40 being, for the most part, associated with active myocarditis, while the later deaths are due to the dynamic effects of the valvular lesions.<sup>23, 26</sup> The group under discussion would then represent those patients who escape significant myocardial injury but develop, after considerable time, definite evidence of valvular disease and may after years go into heart failure as the result of the hydro-dynamic effects of the valvular lesions.

This same reasoning can also account for the long duration among those patients who gave a previous history of definite rheumatic infection. Bland and Jones,<sup>27</sup> in considering the delayed appearance of heart disease among young people following acute rheumatic fever, have expressed the opinion

that continued rheumatic activity is necessary. It does not seem to us that such is essential since, as previously stated, valvular deformity might develop as the result of gradual fibrosis over a period of time in the absence of any recurrence of activity.

It has been our impression that from the viewpoint of cardiac disease, the line dividing rheumatic from non-rheumatic-type infections cannot be definitely drawn. The findings of Rantz et al.<sup>25</sup> have already been cited. There have been many papers published which refer to the abnormal electrocardiograms occurring in patients suffering from streptococcal and other types of infection.<sup>28, 29, 30</sup> The question as to how often such findings are due to a process identical with rheumatic heart disease cannot be answered. We are inclined to agree with Rantz et al. in the view that following streptococcal infections the process may be identical with that following typical rheumatic fever. A long term follow-up of such cases will be necessary to determine how often chronic valvular lesions develop.

### CLINICAL COURSE

In studying the clinical course of these patients, it was thought that the age at which the patient was first informed of the presence of heart disease might be of interest. Only nine patients had such knowledge before the age of 30 and only one of these before 20. In 84 cases, this knowledge was acquired after the age of 40 and 45 of these were 50 years of age or over, at the time. In the great majority, the diagnosis was first made at the time a physician was consulted because of cardiac symptoms. However, in 34 patients the diagnosis was incidental to physical examination for some other reason. In two cases, the diagnosis was first made at autopsy.

The age at which clinical symptoms became manifest was also late. There were a number of patients who had complained of various subjective symptoms over a period of many years. It is difficult to decide whether these complaints were of functional or organic origin. In only four persons did the symptoms begin before 30. In 10, the onset was in the fourth decade, in 41 in the fifth, while in 31, symptoms first appeared in the sixth decade. Two patients first became symptomatic after reaching 60, while 18 never admitted any cardiac symptoms. Therefore, a total of 50 patients reached the age of 50 years without subjective manifestations of heart disease. The average age at the time symptoms appeared in the 88 patients was 46.2 years. Occasionally many years elapsed between the diagnosis of valvular disease and the onset of symptoms. In four of these patients, this period ranged from 18 to 25 years. These facts emphasize the comparatively benign character of the valvular disease in these patients.

The nature of the symptomatology did not differ from that noted in mitral stenosis in general. Shortness of breath, palpitation, and fatigue were usually the first symptoms noted. Exceptions occurred in four instances where hemiplegia, vertigo, hemoptysis, and acute coronary throm-

bosis were the first manifestations. Congestive heart failure had occurred in exactly one-half<sup>53</sup> of these patients up to the date of our last information.

Hemiplegia was common, having occurred in 13 patients. This was probably an embolic manifestation in most instances and related to the high incidence of auricular fibrillation. However, five of these patients were never known to have had auricular fibrillation. Neither did they have hypertension.

Both subacute bacterial endocarditis and clinical evidence of coronary disease were rare. Each condition was noted only once among the 106 cases. Levine<sup>31</sup> has stressed the fact that subacute bacterial endocarditis is rare in the presence of advanced mitral stenosis and auricular fibrillation. The same author<sup>32</sup> emphasized the infrequent association of coronary disease with mitral stenosis.

Of particular interest has been the frequent association of chronic non-tubercular pulmonary disease with mitral stenosis in these older patients. Not infrequently such patients may present themselves with symptoms and clinical findings typical of chronic asthmatic bronchitis. In 29 patients of the present series, the pulmonary findings were sufficiently impressive to be included in the final diagnosis. The diagnosis was emphysema in 22, pulmonary fibrosis in five cases, while the diagnosis of chronic bronchitis was made twice. The chest roentgen-ray plates were available in 81 cases. A review of these disclosed evidence of emphysema or abnormal bilateral fibrosis in 66 instances.

Parker and Weiss<sup>33</sup> have given an excellent description of the structural changes brought about in the lungs as a result of the chronic pulmonary hypertension and congestion resulting from mitral stenosis. They demonstrated subintimal thickening with fibroblastic proliferation, as well as both intimal and medial thickening of the small vessels. Marked changes in the alveolar walls interfere with gaseous exchange and cause stiffening of the lungs. Gouley<sup>34</sup> has stressed the rôle of repeated episodes of pneumonitis and infarction in bringing about chronic pulmonary interstitial changes which interfere with normal respiratory efficiency. Ferguson et al.<sup>35</sup> have discussed the vascular changes which are responsible for hemoptysis. It is obvious that the pulmonary pathologic changes incident to long standing mitral stenosis can be responsible for a severe degree of dyspnea, cough, wheezing, and hemoptysis. It has been our impression that these manifestations are more frequently noted among these older patients.

The associated pulmonary changes also add to the difficulty of diagnosis. The presence of emphysema tends to suppress the intensity of the murmur of mitral stenosis, while the noisy wheezing breath sounds further handicap auscultation. Under such circumstances, very careful examination may be necessary to detect the diastolic murmur, and it may be impossible. Another source of error is the evidence of right heart failure in the presence of marked pulmonary disease which may be interpreted as being due to chronic cor pulmonale. This is particularly true in patients beyond the age of 50.

Such a mistake was made in two of the cases in this series, the correction being made later. It is apparent that the pulmonary disease may contribute to an increase in pulmonary hypertension so that the cardiac failure may actually have a dual etiology.

The incidence of malignancy as an associated disease was quite high. Nine cases were so affected. The relatively large Tumor Service in this Hospital is undoubtedly responsible.

Forty-four of the 106 patients were known to be dead at the time these data were assembled; 47 were known to be living. Contact had been lost with 15 of the patients.

The average age at death was 52.8 years, the oldest patient being 64 years of age. In 14 cases we cannot be certain regarding cause of death since death occurred away from the Hospital. In 19 of the remaining 30 cases, death was due to congestive failure. Embolic episodes accounted for six deaths, five were cerebral, and one was renal in location. Each of the following accounted for one death: subacute bacterial endocarditis, pneumonia, carcinoma of the stomach, carcinoma of the bronchus, and carcinoma of the cecum. Therefore, in 26 of the 30 cases, death was directly related to the heart disease. The duration of congestive failure was known in 18 of the 19 cases and varied from six months to 10 years (average: three years). This corresponds to statistics recorded by other observers based on studies conducted on cases in younger age groups.

It was also impressive to note that many of these patients had engaged in arduous occupations over a period of many years. As previously stated, the onset of symptoms occurred relatively late; and this was in spite of the fact that they had been subjected to considerable physical strain. Some of those who had not developed cardiac symptoms were still very active. This emphasizes that the myocardium was capable of maintaining an excellent reserve over a long period and indicates that there exists a distinct difference in this respect in the disease as seen in these older patients and that which is prevalent in younger persons.

#### PHYSICAL FINDINGS

The characteristic mid-diastolic murmur of mitral stenosis was made a requirement for the inclusion of a living patient in this series. We have included two cases in which the diagnosis was made at autopsy in which no diastolic murmur was described during life. In one of these cases, repeated auscultation had been carried out by several members of the Cardiac Section because it was suspected that such a lesion might be present. In one case, death was due to carcinoma of the cecum and mitral stenosis was an incidental postmortem finding. No special attention had been directed to the heart; and in the admission examination, no abnormal cardiac findings were recorded. Due to the basis upon which these patients were chosen, no information relative to the frequency with which "silent" mitral stenosis is encountered in patients of this age is available. It was found by Flaxman<sup>36</sup>



that no murmur was present in 3.37 per cent and only a systolic murmur was noted in 15.2 per cent of the series of mitral stenosis cases which he reviewed. Such statistics will vary in accordance with the frequency of the examinations and skill of the examiners.

There are several factors which are commonly present in these older people which make the detection by auscultation of the murmur of mitral stenosis more difficult. Obesity is frequently encountered and the layer of fat tends to absorb the low-pitched vibrations of mitral stenosis. Loud, harsh, systolic-apical murmurs are frequent and make the detection of the low-pitched, distant, diastolic murmur, which follows it, difficult. Such harsh systolic murmurs also tend to obliterate the "snapping" quality of the first sound at the apex. Chronic asthmatic bronchitis, emphysema, and fibrosis, also impair the efficiency of auscultation. A very important factor is the failure to consider the possibility of mitral stenosis in the older patients which results in inadequate auscultation.

Cardiac enlargement was definite in the majority of the cases. A review of the roentgen-ray findings disclosed 68.4 per cent of the cases showing definite cardiac enlargement. Borderline hearts were placed in the normal group. The degree of cardiac enlargement was frequently quite marked when compared to that usually seen in young persons with stenosis of the mitral valve alone. This was usually due to the prominent left ventricular enlargement. It is believed that the tendency toward left ventricular enlargement and the frequency of loud, harsh, apical-systolic murmurs are related. In turn, both of these may be related to the characteristics of the evolution of valvular lesions in these older patients. The relatively low grade rheumatic infection may cause a slow progressive deformity in which adherence of the cusp margins is less marked. As a result, mitral insufficiency becomes a prominent physiological component. This situation existing over a period of years may well account for the fact that the left ventricular enlargement is greater than that usually seen in the more rapidly developing, tight, mitral stenosis common to younger people.

Hypertension also plays a part in the left ventricular enlargement, though it was not present as frequently in our series as in that reported by Levine and Fulton.<sup>7</sup> Levine has repeatedly emphasized the frequency of hypertension in these older patients with mitral stenosis. In this series, the blood pressure of only 32 patients was found to exceed 150 systolic or 90 diastolic. In only 18 did the diastolic pressure exceed 100. Levine and Fulton<sup>7</sup> noted that the blood pressure exceeds 150 mm. of mercury systolic and 100 diastolic in 58 per cent of cases of mitral stenosis over 45 years of age. Boas and Fineberg<sup>6</sup> indicate that hypertension was present in 24 of 46 patients who had passed 50 years of age. However, Horns<sup>8</sup> noted hypertension in only 30 per cent of the patients 45 years of age or over, which is comparable to this group. Among the 32 patients with hypertension, marked cardiac enlargement was present in 20. A similar degree of enlargement was noted in only 21 of the 75 patients with normal blood pressure.

The rhythm was a regular sinus mechanism in 45, while chronic auricular fibrillation existed in 60 patients. Persistent auricular flutter was present in one case. Lewis<sup>37</sup> stresses the fact that the frequency of auricular fibrillation increases with age among patients with mitral stenosis. White<sup>14</sup> states that over 50 per cent of adult cases of mitral stenosis have auricular fibrillation. Boas and Perla<sup>1</sup> noted this arrhythmia in 56.5 per cent of 47 patients with mitral stenosis who were past 50. Garvin<sup>38</sup> found auricular fibrillation to be more frequent among older patients with rheumatic heart disease; however, his statistics reveal an incidence of 44 per cent among patients over 50 as compared to 51.2 per cent for the entire series. de la Chapelle et al.<sup>24</sup> also found the incidence increased among the older patients.

It is our impression that the auricular fibrillation of mitral stenosis is more closely correlated with auricular distention than with any other factor and that its incidence increases steadily with the period of time over which auricular strain has been present. There was a definite history of rheumatic fever in 14 of the patients who had auricular fibrillation. The elapsed period from this date to death or last examination was 32.2 years. Brill<sup>39</sup> has expressed a similar opinion relative to the etiology of this arrhythmia in association with coronary disease.

The relation of auricular fibrillation to embolic manifestations in patients with rheumatic heart disease has been stressed by Weiss and Davis<sup>40</sup> and by Harris and Levine.<sup>41</sup> Such a relationship was not striking in this small series. Only 10 of the 18 patients who suffered from definite embolic episodes had auricular fibrillation.

The character of the heart sounds was not significantly different from that usually noted with mitral stenosis. The first sound at the apex was accentuated in 72 of the 99 patients in whom the description of sounds was recorded. The pulmonary second sound was considered to be accentuated in 33 instances, while the aortic second sound was described as accentuated in five patients. The quality of the first apical sound was of diagnostic value in these older patients. The "opening snap" of the mitral valve should be mentioned. Margolis and Wolferth<sup>42</sup> have pointed out its value in diagnosis. It was occasionally of value in this series of cases particularly when the patient was first seen in the presence of rapid auricular fibrillation.

## DIAGNOSIS

It is generally agreed that diagnosis of mitral stenosis is fundamentally dependent upon hearing the characteristic murmur. The variations in the murmur have been described by Lewis,<sup>37</sup> White,<sup>14</sup> and Fishberg.<sup>43</sup> There is nothing to add but we wish to emphasize that the murmur may be audible only in a localized area and also that auscultation must be carried out with mitral stenosis in mind. We have already discussed factors commonly present in the older patients which add to the difficulties of auscultation.

There is one other point which bears some comment. Fisher<sup>44</sup> and

Wood and White<sup>45</sup> years ago discussed the mid-diastolic rumble heard in older patients with enlarged hearts while in failure. More recently others have made similar observations.<sup>46, 47</sup> In our experience such murmurs are not uncommon when auscultation is done carefully with the patient reclining on his left side. These murmurs, while definite, do not usually have the typical characteristics of mitral stenosis. They are usually somewhat higher in pitch, softer and less rumbling in quality. Likewise, the sharp presystolic crescendo quality is lacking in the presence of sinus rhythm. However, these points are of little practical value since in mitral stenosis the murmur may lose its characteristic attributes or become inaudible during congestive failure. It is our impression that this occurs more commonly among the older patients. When a patient is first encountered in congestive failure and such a diastolic apical murmur is present, it is impossible to be certain as to the existence of mitral stenosis. However, as compensation is restored, the murmur increases in intensity and becomes more characteristic in the presence of organic mitral stenosis, otherwise it fades away with restoration of compensation.

A sharply accentuated first apical sound in the presence of congestive failure favors mitral stenosis since in the degenerative types of heart disease this sound is commonly of poor quality and of less intensity than the second heart sound. This principle may be altered in mitral stenosis, however, if there is present a loud harsh systolic murmur which tends to obscure the first sound. Accentuation of the pulmonary second sound is of no value in the presence of congestive failure unless it is marked. The "opening snap" of the mitral valve, if present, is of value under these circumstances.

The roentgen-ray films of the chest were reviewed as to their value in the diagnosis of mitral stenosis. In 36 of the films, the cardiac configuration was found to be quite typical of mitral stenosis. In eight instances there was some prominence of the pulmonary conus which was suggestive of this diagnosis. The remainder were of no diagnostic assistance. We do not have adequate data on the fluoroscopic findings to be worthy of comment.

Electrocardiograms had been made on 104 of the 106 patients. A review of the findings revealed that there was a definite tendency toward right axis deviation in 35 instances. This deviation was marked in only 10 of the total. Left axis deviation was less common; however, quite marked deviation to the left was present in 12 persons. Hypertension was associated with left axis deviation in the great majority. In approximately one-half the cases there was no significant deviation of the electrical axis. Bundle branch block was noted in five cases, left in three, and in two, it was right. T-wave and S-T segment changes were common, most of this being due to digitalis. In two patients; the P-R interval was prolonged and in one case complete heart block existed with auricular fibrillation. The electrocardiograms did not prove to be of any great value in diagnosis. The presence of right axis deviation in patients of this age should suggest the possibility of mitral stenosis but no further help can be expected.

The most important single factor in diagnosis is the matter of bearing in mind the possibility of mitral stenosis in the older patient. There are several clinical observations which we have found helpful in suggesting this diagnosis.

1. The presence of auricular fibrillation.
2. An accentuated sharp first sound at the apex, particularly in the presence of heart failure.
3. Unusual accentuation of the pulmonary second sound.
4. A long history of chronic pulmonary symptoms; mitral stenosis should be excluded before a diagnosis of chronic cor pulmonale is made, particularly if auricular fibrillation is present.
5. Right axis deviation in the electrocardiogram even though it is slight.
6. Repeated episodes of congestive failure over a long period of time. Complaints referable to liver distention are prominent in the presence of mitral stenosis.
7. Atypical apical diastolic murmurs heard during congestive failure. These should be carefully followed.

The presence of any of the above observations should stimulate careful examination and study which may reveal mitral stenosis which might be otherwise overlooked in a patient of advanced years.

#### SUMMARY

A study of the clinical course and findings in 105 patients with isolated mitral stenosis who survived the age of 50 has been made.

The high incidence of a negative history of rheumatic fever is thought to be due to these patients having suffered from atypical "rheumatic type" infections during which cardiac damage was done.

Our information indicates that the advanced age of these patients is associated with an unusually long course of rheumatic heart disease. This long course can be explained by a fundamental difference in the pathogenesis of the rheumatic process within the heart in contrast to that occurring in younger persons with a shorter duration. A relatively slight involvement of the heart limited for the most part to the endocardium and mitral valve would allow the development of mitral stenosis with the myocardium being spared. Under these circumstances, the heart is able to maintain compensation over a period of many years, and in many instances to tolerate active physical exertion.

The great frequency of symptoms and physical findings of non-tuberculous pulmonary disease was striking in these patients. It is our opinion that the longer the patients with mitral stenosis live the greater will be the incidence of chronic pulmonary disease.

The incidence of auricular fibrillation was high and is believed to be related to the duration of auricular strain. Embolic manifestations were frequent, occurring in the absence of, as well as with auricular fibrillation.

Hypertension was not as common in this group of patients as has been reported by other writers. It apparently was a factor in causing a marked degree of cardiac enlargement in many instances. It is not believed that the longevity of these patients is dependent upon the presence of hypertension as has been suggested.

Factors which are commonly present in these older patients and add to the difficulty in diagnosis are discussed. Failure to consider the possibility of mitral stenosis is thought to be the most common cause for error in diagnosis among older patients. Certain clinical observations which should suggest this possibility are outlined.

The majority of deaths in this series were due to the cardiovascular disease present. In approximately two-thirds of the fatal cases death was from congestive failure. Once congestive failure occurred, the course was essentially the same as that seen in younger patients.

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# CASE REPORTS

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## THE CARDIOVASCULAR MANIFESTATIONS OF INDUCED THYROTOXICOSIS; REPORT OF TWO CASES \*

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THE occurrence of cardiovascular manifestations as results of induced thyrotoxicosis has not been commonly recorded. It is the purpose of this paper to report two cases in which the ingestion of excessively large doses of desiccated thyroid substance was associated with cardiovascular manifestations. The evidence to be presented leaves no reasonable doubt that these changes were the results of induced thyrotoxicosis.

### CASE REPORTS

*Case 1.* The patient was a white female 63 years old, first examined on November 26, 1940. For two months previously dyspnea, which had increased in severity, had been observed. Palpitation, nervousness and tremor had been noted for the same period. Frequency of urination was present. The medical history was irrelevant. Further questioning revealed that for two years previously 2 grains (0.13 gm.) of desiccated thyroid substance had been administered daily to the patient. The dosage, however, had been increased by the patient without consulting a physician, so that during the previous year she had been taking 8 grains (0.52 gm.) of desiccated thyroid substance daily.

The physical examination revealed an acutely ill, markedly dyspneic white female. The temperature was 98° F. (36.6° C.), and the pulse rate, which was grossly irregular, was 180 beats per minute. The blood pressure was recorded as 160 mm. of mercury systolic and 70 mm. diastolic. No palpable enlargement of the thyroid gland could be demonstrated. Moist râles were heard over the base of the right lung. No cardiac murmurs were heard. The abdomen was normal. A fine tremor of the fingers was present. Auricular fibrillation was confirmed by the electrocardiogram (figure 1a). Roentgenographic examination of the thorax revealed no evidence of a substernal thyroid gland. The heart was slightly enlarged; its greatest transverse diameter was 14 cm. as compared with the diameter of the thorax, which was 26 cm.

Results of examination of the urine and of a complete blood count were normal. The basal metabolic rate was +36 per cent. The value for cholesterol was 157 mg. per 100 c.c. of plasma.

In view of the evidences of congestive heart failure, the patient was confined to bed and 5 minims (0.31 c.c.) of strong solution of iodine (Lugol's solution) was administered three times daily. Administration of desiccated thyroid substance was discontinued. Auricular fibrillation continued for six days, at the end of which there was a return to normal rhythm. There was an associated abatement of the dyspnea, palpitation and tremor, and basal metabolism became normal. On the seventh day, however, auricular fibrillation reappeared and persisted for 12 hours; it was then replaced by a regular rhythm, with a pulse rate of 160 beats per minute. An electro-

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cardiogram was not made at this time, but auricular flutter was considered to be present.

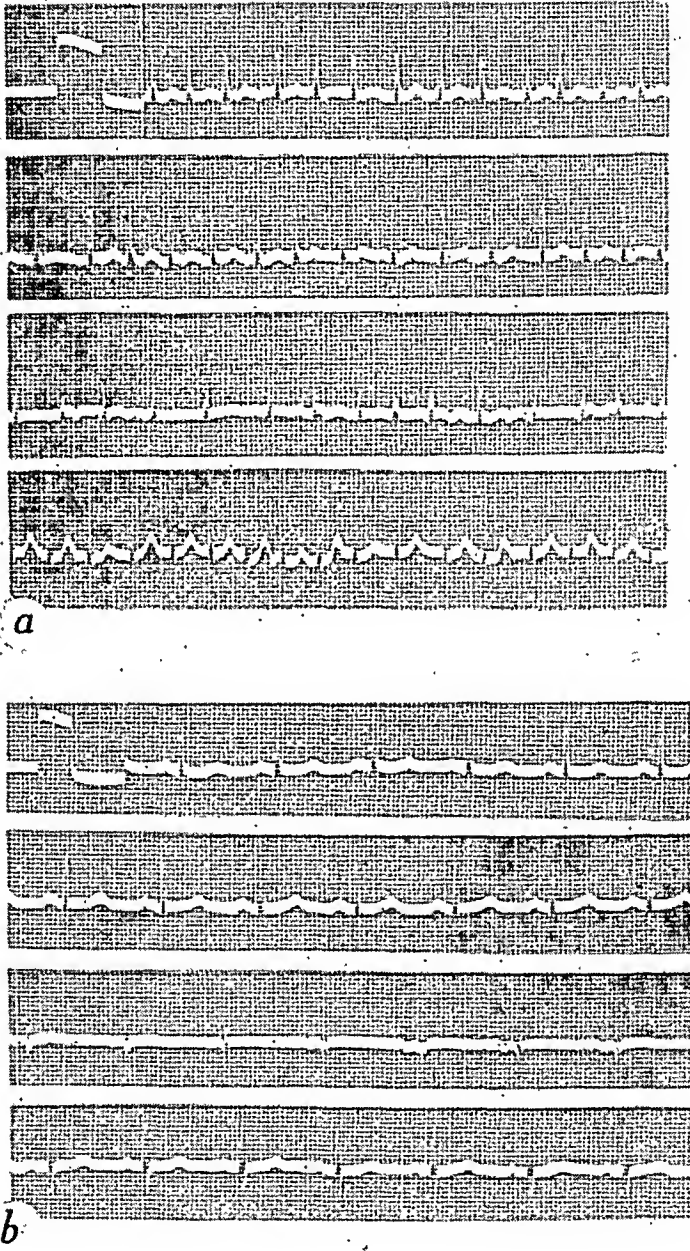


FIG. 1a. Auricular fibrillation occurring during the period of induced thyrotoxicosis in case 1; b, normal electrocardiogram after discontinuance of the taking of desiccated thyroid substance in case 1.

On December 6, 1940, eight days after the first examination of this patient, normal sinus rhythm again was present (figure 1b). The patient remained well through the day and complained of nothing. At 8:15 on the evening of the same day, the patient was examined: the pulse rate was regular, with a rate of 68 beats per minute;



the blood pressure was 130 mm. of mercury systolic and 80 mm. diastolic; results of examination of the heart were normal. Five minutes later the patient was found unconscious, critically ill, with left hemiplegia. It was felt that she had suffered cerebral embolism secondary to intracardiac thrombosis and induced thyrotoxicosis.

During the next 24 hours the temperature of this patient increased to 101° F. (38.3° C.), and remained elevated for eight days. The pulse rate varied from 70 to 90 beats per minute, and it was always regular. The comatose state persisted for five days, as did complete left hemiplegia. The general condition of the patient gradually improved, and she was discharged from the hospital on January 1, 1941, 35 days after she had been admitted.

For the next three months there was gradual improvement in the condition of the patient, and at the end of this time some degree of function had returned to the left leg. Since then, and to the time of this report (a period of five years), the patient has been observed at frequent intervals. Results of all examinations of the heart have been normal. The pulse rate has been regular, varying from 68 to 80 beats per minute. Auricular fibrillation has not returned during this period, and repeated electrocardiograms have revealed normal sinus mechanism. The blood pressure has been normal, and there has been no recurrence of congestive heart failure. Orthopedic care has produced marked improvement in walking, but little improvement in the function of the patient's left arm has been noted.

In this case all the manifestations of thyrotoxic heart disease, including congestive heart failure, auricular fibrillation and probable cerebral embolism followed the ingestion of excessive amounts of desiccated thyroid substance over a period of one year. On the basis of the history of this patient, it appears that prior to the onset of congestive heart failure, auricular fibrillation and cerebral embolism, heart disease had not been present. In the five years subsequent to the episode of auricular fibrillation and cerebral embolism—at which time the taking of desiccated thyroid substance was discontinued—there has been no further evidence of heart disease. It seems probable that all the manifestations of heart disease in this case can be attributed to the use of desiccated thyroid substance in excessive amounts, because they appeared after prolonged use of this substance and disappeared after discontinuance of the use of the substance. Cerebral embolism probably arose from the development of mural thrombosis within the left side of the heart as a result of congestive heart failure and auricular fibrillation.

*Case 2.* The patient was a white female 60 years old, first examined on January 29, 1945. At that time the chief signs and symptoms were lightheadedness, vertigo and the sudden onset of irregular, rapid heart action. For several years this patient had been taking desiccated thyroid substance in doses of 2 to 3 grains (0.13 to 0.19 gm.), for myxedema. The dosage of desiccated thyroid substance had been increased by the patient to 7½ grains (0.49 gm.) taken daily, several weeks before I saw her. Slight dyspnea was present. The medical history was irrelevant. No evidence of thoracic pain in the past or present could be elicited.

The results of physical examination revealed an elderly white female who had moderate dyspnea and who manifested apprehension. The pulse rate was 140 beats per minute, and was grossly irregular. The temperature was 98° F. (36.6° C.) and the blood pressure was 140 mm. of mercury systolic and 80 mm. diastolic. There was no demonstrable enlargement of the thyroid gland. Auricular fibrillation was present. A systolic murmur was heard over the pulmonic area. The lungs, abdomen and extremities were normal.

Results of examination of the urine and of the Kahn test were normal. The sedimentation time and blood count were within normal limits. The transverse diameter of the heart was 13.5 cm.; the transverse diameter of the thorax was 27 cm. There was no roentgenologic evidence of a substernal thyroid gland. An electrocardiogram revealed auricular fibrillation, with left bundle-branch block (figure 2a).

The patient was confined to bed and the administration of thyroid extract was discontinued. Strong solution of iodine (Lugol's solution) and digitalis were ad-

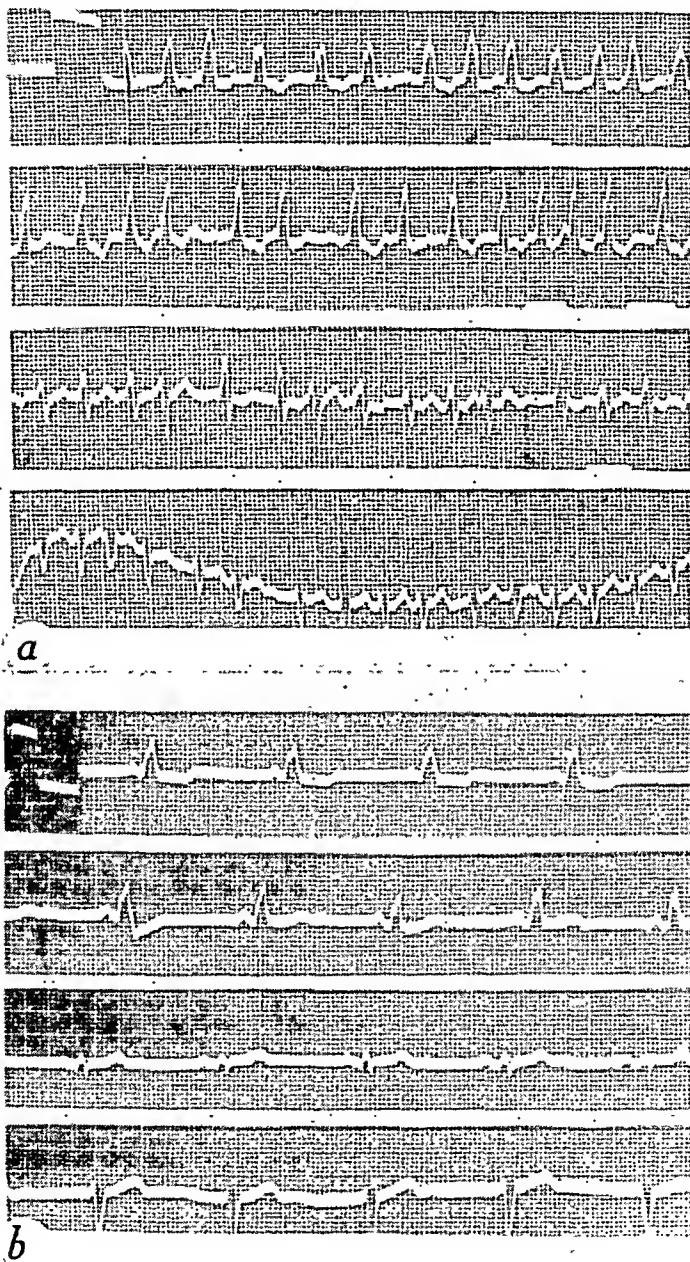


FIG. 2a. Auricular fibrillation and left bundle-branch block during the period of induced thyrotoxicosis in case 2; b, sinus mechanism and persistence of left bundle-branch block after discontinuance of the taking of desiccated thyroid substance in case 2.

ministered. Approximately 48 hours after the first examination of this patient, spontaneous resumption of normal sinus rhythm occurred. An electrocardiogram made one day later revealed sinus mechanism with persistence of left bundle-branch block (figure 2b).

During the next year this patient was observed at intervals. At no time subsequently was irregular heart action present, and to the time of this report there has been no dyspnea, pain in the thorax or palpitation. The pulse rate and blood pressure have been normal. After discontinuance of the taking of desiccated thyroid substance, evidence of myxedema associated with a basal metabolic rate of  $-25$  per cent appeared. The administration of desiccated thyroid substance in a dosage of 1 grain (0.06 gm.) daily was resumed without harmful effects.

In this case auricular fibrillation accompanied by dyspnea and palpitation was observed after the ingestion of excessive amounts of desiccated thyroid substance. These manifestations of thyrotoxic heart disease disappeared promptly after the administration of desiccated thyroid substance had been discontinued, and they have not reappeared to the time of this report. In this instance it is probable that the presence of bundle-branch block is evidence of coronary artery disease, and that an excessive amount of desiccated thyroid substance was sufficient to produce auricular fibrillation in a heart that exhibited evidence of previous disease. This is in contrast to the situation in the first case, in which no evidence of preëxisting or underlying heart disease could be demonstrated.

#### COMMENT

Two cases are presented in which the manifestations of thyrotoxic heart disease with auricular fibrillation were observed after the ingestion of large amounts of desiccated thyroid substance. In both cases discontinuance of the taking of desiccated thyroid substance resulted in prompt resumption of normal sinus rhythm. Hurxthal<sup>1</sup> has reported one case in which auricular fibrillation followed self-induced hyperthyroidism. Thyrotoxicosis may be the sole cause of heart failure,<sup>2,3</sup> or the effect of thyrotoxicosis may be superimposed on organic heart disease of other causation, producing the manifestations of heart failure.<sup>4,5</sup> In the first case reported herein the only demonstrable cause of congestive heart failure, auricular fibrillation, intracardiac thrombosis and cerebral embolization was thyrotoxicosis induced by the ingestion of desiccated thyroid substance. In the second case thyrotoxicosis was superimposed on coronary artery disease, with resulting auricular fibrillation.

It has been recorded that women tolerate thyrotoxicosis less well than men.<sup>3</sup> In both of the present two cases of induced thyrotoxicosis with cardiovascular manifestations the patients were women. Advancing age also favors the development of heart failure and auricular fibrillation in thyrotoxicosis.<sup>4</sup> The respective ages of the two patients reported on herein were 63 years and 60 years. Elderly people likewise are affected more readily than younger persons by thyroid extract, and when this extract is administered, it should be given with caution. It has been shown in this report that desiccated thyroid substance may, in the aged, produce the clinical manifestations of thyrotoxic heart disease without underlying heart disease, or the manifestations of thyrotoxic heart disease may, in turn, be superimposed upon coronary artery disease. Among elderly persons the manifestations of thyrotoxic heart disease in the absence of demonstrable thyroid enlargement should raise the question of induced hyperthyroidism.

## SUMMARY

Two cases have been presented in which evidence of thyrotoxic heart disease appeared after the ingestion of excessive doses of desiccated thyroid substance. In the first case there was no preëxisting heart disease, and probable cerebral embolism and hemiplegia on the left occurred after a period of congestive heart failure with auricular fibrillation. The second case was complicated by coronary artery disease, and auricular fibrillation appeared for the first and only time after the ingestion of large amounts of desiccated thyroid substance. In both cases auricular fibrillation and other evidence of thyrotoxic heart disease disappeared promptly after discontinuance of the administration of desiccated substance.

## CONCLUSIONS

Among older persons desiccated thyroid substance may produce the manifestations of thyrotoxic heart disease, including auricular fibrillation and embolism. The patient who presents evidence of thyrotoxic heart disease, in the absence of demonstrable goiter, should be questioned as to self-medication with desiccated thyroid substance.

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## ACUTE FEBRILE ANEMIA AND THROMBOCYTOPENIC PURPURA WITH VASOTHROMBOSES \*

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AN acute syndrome, characterized clinically by fever, anemia, thrombocytopenic purpura, renal, cardiac, and neurological manifestations, and pathologically by thrombotic lesions occluding arterioles, capillaries, and venules in almost every organ and tissue, was described by Baehr, Klemperer and Schiffrin in 1936.<sup>1</sup> Moschcowitz<sup>2</sup> described a case with similar pathological finding but without purpura in 1925. To date only seven cases have been recorded in the

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literature, five from the Mt. Sinai Hospital in New York.<sup>1, 2, 3, 4, 5</sup> This number from one hospital suggests that the disease is a good deal more common than the literature would indicate, and that it is not being recognized elsewhere. For this reason we feel justified in reporting another case, in which the diagnosis was made before death. Further, although neurological manifestations have been prominent in all the cases reported, no neuropathological examinations have been reported. Complete examination of the central nervous system was available in this case.

#### CASE REPORT

L. H., a 15 year old colored school girl, was admitted to the Cincinnati General Hospital on February 8, 1944, following the acute onset eight days earlier of sore throat, fever, headache, vomiting, hematuria and petechial eruption. The patient had enjoyed good health in the past except for frequent upper respiratory infections and for a single generalized convulsion at the age of 12. On January 31 she noted onset of nasal discharge, sore throat, some fever, and slight lower abdominal pain. On February 1, a physician prescribed sulfathiazole, 0.5 gm. every four hours, of which she took a total of 10 gm. There was no improvement and tender lymph nodes developed at the angles of the jaw. On February 6 she began to have more periumbilical and lower abdominal pain, and a second physician found tenderness in the right lower quadrant and gave more sulfathiazole (0.5 gm. every four hours for two days). She seemed to grow rapidly worse, developed headache, puffiness of the face, gross hematuria, red spots over face and chest, blurring of vision and delirium. On February 8 she became unconscious and was admitted to the Contagious Division.

*Physical Examination:* Temperature was 104.2° F.; pulse 136; respirations 32; blood pressure 120 mm. Hg systolic and 56 mm. diastolic. The patient was a well-developed and well-nourished colored girl, severely ill, unconscious, but responding to painful stimulation. Respirations were regular, deep and not embarrassed. The skin and mucous membranes were very pale, and scattered over the chest, abdomen and thighs were a moderate number of pin-head sized petechiae. There was slight periorbital edema and the conjunctivae were pale. The pupils were regular, equal, reacted promptly to light. Examination of the fundi revealed several large hemorrhages, some of which had white centers. The optic discs and retinal vessels were normal. The nasal mucous membranes were inflamed, and there was a mucopurulent discharge. The tongue was thickly coated. The buccal mucous membranes were pale, with several petechiae. The pharynx was slightly injected and some bloody phlegm was adherent to it. The neck was supple. The lungs were clear. The heart was not enlarged and no murmur was heard. The abdomen was flat, soft, and non-tender. Pelvic examination was not done (patient menstruating). All deep tendon reflexes were absent except for the ankle jerks.

*Laboratory Data on Admission:* Hemoglobin, 5.2 gm.; red blood cells, 1,490,000 per cu. mm.; white blood cells, 52,500 per cu. mm.; differential: Polymorphonuclear leukocytes, 84 per cent, basophiles, 1 per cent, lymphocytes, 13 per cent, monocytes, 2 per cent; there were 18 normoblasts per 100 white blood cells. The red blood cells revealed marked anisocytosis and poikilocytosis. There was no sickling of the red cells. A catheterized urine specimen had a specific gravity of 1.015, pH 5.5, albumin 4+; 3 to 4 white cells, 50 red cells, and a few granular casts per high power field. The blood urea nitrogen was 28 mg. per 100 c.c. A blood culture was negative. Agglutination for brucella was positive to a dilution of 1/320; Weil-Felix reaction was negative. The blood Wassermann reaction was negative. Lumbar puncture revealed an initial pressure of 220 mm. H<sub>2</sub>O, final pressure of 150 mm. H<sub>2</sub>O; the fluid was clear, contained 2 white blood cells per cu. mm., protein content was 32

mg./100 c.c.; sugar, 73 mg./100 c.c.; chloride, 726 mg./100 c.c.; Wassermann reaction, negative; culture, negative.

*Teleoroentgenogram of Chest:* Several calcifications were seen in either hilum. An irregular calcification about 1 cm. in diameter appeared in the right lower lung field. No definite area of infiltration was seen. The cardiac diameter was 14.5 cm. in a chest of 24 cm. diameter.

*Course:* Upon admission the patient was thought to be suffering from sepsis. Her course was stormy during the first week. The temperature ranged between 102 and 104° daily, pulse was compatible, and she was delirious. She was given sulfadiazine, 1 gm. every four hours, and on the third day this was changed to sulfamerazine. She also received five blood transfusions and intravenous glucose and saline. Several times she coughed up some bright red blood or blood tinged mucus, but examination of the lungs revealed no abnormalities. On the fifth day she was transferred to the medical service. At that time the physical examination was unchanged except that slight icterus was now noted and the icteric index was 12. The patient still appeared critically ill. Gallop rhythm was present. New petechiae continued to appear. Posterior cervical lymph nodes were enlarged and tender. Blood count on the third day was as follows: Red blood cells, 1,680,000 per cu. mm.; hemoglobin, 5.2 gm.; white blood cells, 33,250 per cu. mm.; differential, polymorphonuclear leukocytes 71 per cent, lymphocytes, 11 per cent, monocytes, 4 per cent, metamyelocytes, 9 per cent, "C" myelocytes 5 per cent, 43 normoblasts per 100 white blood cells. The red cells revealed marked anisocytosis, poikilocytosis, and microcytosis; reticulocytes were 11.6 per cent. The platelet count was 10,800 per cu. mm. The urine continued to show 2+ to 4+ albumin, red cells, white cells, casts, and the specific gravity was 1.012 to 1.015. At the end of a week, after a number of blood transfusions, the hemoglobin had risen to 8.0 gm./100 c.c.

An electrocardiogram on the sixth day revealed sinus rhythm, PR 0.19 sec., QRS 0.11 sec., all T-waves low voltage. Sulfamerazine was discontinued on the fifth day, and the blood level was 7.5 mg. per cent on the sixth day. During the subsequent two days the patient showed much improvement and by the ninth day temperature had fallen to normal. On the seventh day platelets had risen to 133,400, and white blood count had fallen to 12,650. A sternal aspiration revealed bone marrow that was hyperplastic for the erythroid series and megakaryocytes were present in normal numbers. No abnormal cells were seen. Petechiae disappeared, eyegrounds began to clear and mental status returned to normal. Gallop rhythm was still present when the patient sat up. Three electrocardiograms during the second week continued to show abnormalities (sinus tachycardia, PR 0.16–0.26 sec., QRS 0.10–0.12 sec., inverted T<sub>1</sub> and T<sub>4</sub>, diphasic T<sub>2</sub>, depressed ST<sub>2</sub>). Icteric index fell to 6 and blood urea nitrogen to 13 mg. per cent. After the second week albuminuria was no longer found although occasional red cells, white cells and casts remained. Maximum specific gravity was 1.018. The hemoglobin rose to 10.5 gm., but the leukocyte count tended to be low (3,750 to 6,000) and an eosinophilia of 2 to 8 per cent was noted. An electrocardiogram just before discharge still showed prolonged auriculo-ventricular and intraventricular conduction, and low voltage T-waves, but the rate was 60. A teleoroentgenogram of chest on the eighteenth day revealed that the heart measured 12.5 cm. in a chest of 25.5 cm.

The reaction to the various sulfonamides was tested. On the thirteenth day 0.5 gm. sulfathiazole (orally) was followed in four hours by chill, malaise, rise in temperature to 104.2° F, tachycardia (140), confusion, leukocytosis (19,150 per cu. mm.), but no change in hemoglobin, red blood cell count, urine, or icteric index. The reaction cleared entirely in 24 hours. On the eighteenth day 0.5 gm. sulfadiazine was given and resulted in an almost identical reaction (temperature 104.8° F., pulse 140, white blood count 18,000 per cu. mm.) There was no reaction to sulfanilamide (up

to 2 gm.) and a very mild reaction to sulfamerazine. Patch tests with the four sulfonamides were negative. The patient was discharged on the forty-second hospital day, March 21, 1944, 50 days after the onset of her illness.

During the subsequent month the patient was followed in the out-patient department. Subjectively she felt well except for palpitation and some dyspnea. Examination revealed tachycardia but no cardiac murmurs. However, urine always revealed + to ++ albumin, and a few leukocytes and red cells and casts; specific gravity ranged from 1.018 to 1.023. An anemia persisted (red blood count 3.00—3.80 mil. per cu. mm.) and the leukocyte count ranged between 4,600 and 8,000 per cu. mm. On one occasion eosinophilia of 8 per cent was present. An electrocardiogram on March 28, 1944 revealed  $T_3$  inverted, PR 0.16 sec. and on April 18, 1944 PR 0.24 sec. and low voltage T-waves in all leads. The patient received ferrous sulfate as the only medication. On April 25, 1944 the patient noted a sore throat, malaise and fever and a petechial eruption developed. Menstrual bleeding began. She did not improve and two days later was admitted to the hospital.

*Physical Examination:* Temperature was 100° F., pulse 110, respirations 20, blood pressure 112 mm. Hg systolic and 70 mm. diastolic. The patient appeared moderately ill, drowsy, pale, and numerous fresh petechiae were noted over the chest, abdomen, back, extremities, conjunctivae and buccal mucous membranes. Enlarged lymph nodes were felt in the neck and axillae. Examination of the optic fundi revealed several old and recent hemorrhages, but normal retinal vessels. A small superficial necrotic area with dirty gray membrane was noted over the right tonsil and a large hemorrhage was found over the anterior tonsillar fold. The lungs were clear. The heart was enlarged, gallop rhythm was present and a rolling systolic murmur was heard over the base, transmitted to the neck and toward the apex. The second pulmonary sound was louder than the second aortic sound. The abdomen was soft, not tender, and no organs were felt. The deep reflexes were depressed, but no pathological reflexes were elicited. The patient's course was stormy. The temperature gradually rose and by the fourth day was ranging between 102 and 104° F. She received several blood transfusions. Skin purpura, retinal hemorrhages and vaginal bleeding increased, and on the sixth day liver and spleen were noted to be palpable 1 to 2 cm. below the costal margin. She lapsed into coma and the head and eyes were noted to be turned to the right, with spontaneous lateral nystagmus. The right pupil was 6 mm. in diameter and the left pupil 4 mm., and both reacted poorly to light. There was a left central facial weakness, the left arm was spastic and the left leg paretic and flaccid. Plantar reversal signs were elicited on the left. No platelets were observed on the stained blood smear that day. An emergency splenectomy was performed that night. The temperature rose to 106° F. On the next day a right facial weakness was noted, both pupils were dilated and non-reactive and both legs were flaccid and paralyzed. Hemorrhages occluded both optic discs. The patient went into shock and died the following day.

*Laboratory Data:* Hemoglobin, 6.0 to 8.0 gm. per 100 c.c.; red blood cells, 1,550,000 to 2,870,000 per cu. mm.; white blood cells, 10,000 to 48,000 per cu. mm.; differential, polymorphonuclear leukocytes 60 per cent, eosinophiles 2 per cent, lymphocytes, 30 per cent, stab cells 8 per cent; reticulocytes, 3.8 per cent; platelets, 110,000 per cu. mm. There was no sickling of the red blood cells. The bleeding time was 11 minutes, and the clotting time 7 minutes. The fragility test showed a range of 0.26 to 0.38 (normal 0.32 to 0.48). Urine: specific gravity, 1.005 to 1.020; albumin 3+, occasional red cells, white cells and casts. The blood urea nitrogen was 9 mg. per 100 c.c.; icteric index, 16, protein, 6.16 gm. per 100 c.c.; the van den Bergh reaction was moderately positive, prompt diphasic. The Weil-Felix reaction and heterophile agglutination were negative. Urine and blood cultures were negative. A bone mar-

row biopsy revealed hyperplasia in the red cell series with increase in early erythroblasts, while the myeloid elements and megakaryocytes were normal.

An electrocardiogram revealed sinus tachycardia, rate 110; PR interval 0.16 sec.; QRS 0.08 sec.; all T-waves inverted and  $ST_2$  and  $ST_3$  depressed.

*Necropsy Findings:* The necropsy was performed 19 hours post mortem. The body, measuring 162 cm. in length, was that of a well developed and nourished negro

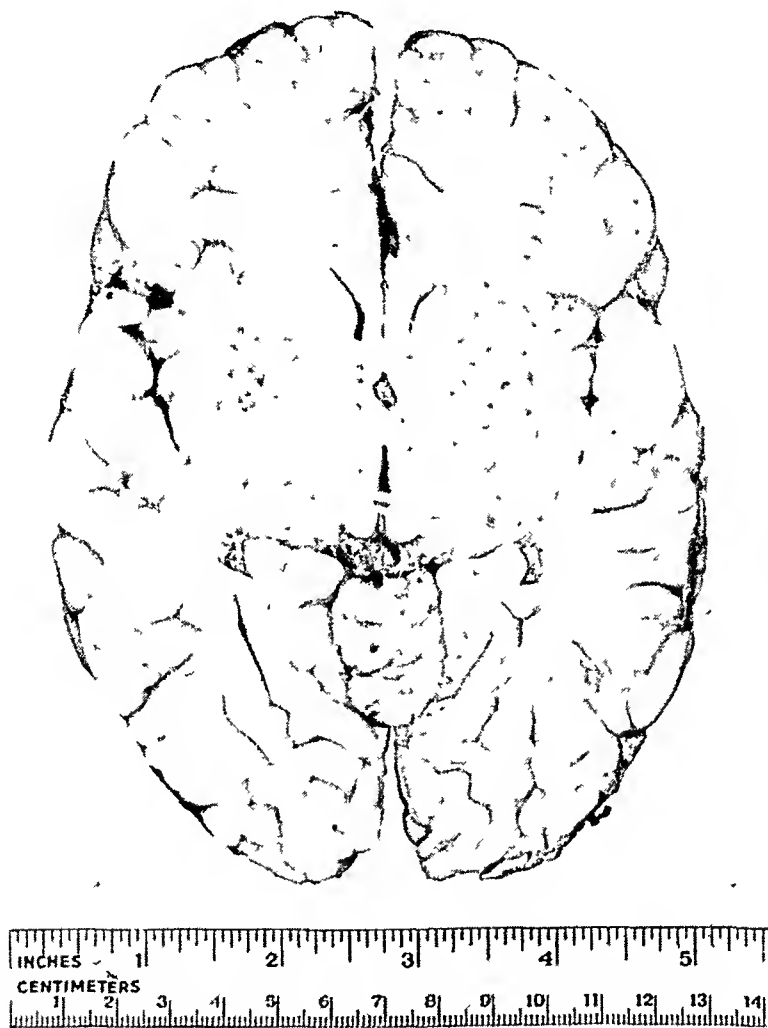


FIG. 1. Horizontal cut through the brain. Note the scattered petechial hemorrhages in the basal ganglia on the left and in the folia of the cerebellum.

girl. Numerous inconspicuous petechiae and purpuric areas were distributed widely over the body. There was an unhealed upper left rectus incision wound measuring 8 cm. in length.

The usual "crutch" incision revealed the absence of the spleen, several black silk sutures in the splenic pedicle, and friable fibrinous adhesions binding the omentum to the pedicle. The peritoneal surface of the left dome of the diaphragm and the serosa of the stomach, small and large intestines presented numerous petechiae. Elsewhere the peritoneum was normally thin, smooth, and translucent. The panniculus was



moderately thick, and the musculature well developed. The remaining viscera of the abdomen were in their usual relations. The slightly enlarged mesenteric and peri-aortic lymph nodes were uniformly firm and light red. The peritoneal cavity contained about 500 c.c. of clear yellow serous fluid. The adult female breasts presented no masses. Removal of the normal breast plate revealed the organs of the thorax in their usual relations. The pleural surfaces over both lungs were normally thin, smooth, and translucent. Each pleural space contained about 500 c.c. of clear yellow serous fluid. The pericardial sac was normally thin and pliable, contained about 400 c.c. of clear yellow serous fluid, and measured 17 cm. in greatest transverse diameter. The chest was 27 cm. wide. The structures of the neck were not examined.

The heart weighed 320 grams and was flabby. The light tan and brown mottling of the myocardium was visible through the normally thin, smooth and translucent epicardium and mural endocardium. The cut surfaces of the myocardium also showed numerous petechiae. The right atrium was dilated. Along the line of closure of each mitral valve leaflet was a row of several red, soft, friable verrucous vegetations measuring up to 2 mm. in diameter. The remainder of the mitral valve leaflets, the chordae tendineae, and the other valves appeared normal. The thin walled, patent coronary arteries showed a few scattered smooth, soft, slightly elevated, yellow, intimal plaques. The aorta and its branches showed no regions of dilatation or narrowing, and the intima of the aorta showed a few scattered, soft, yellow plaques.

The lungs appeared normal in size. The upper lobes of both lungs were mottled light and dark gray, crepitant, soft and elastic. The cut surfaces of these lobes were grayish-pink and relatively dry. The lower lobes of both lungs were dark blue, firm, subcrepitant, and inelastic, and the cut surfaces evenly dark red and dry. The smooth, unbroken mucosa lining the patent bronchi was uniformly reddened. The hilic lymph nodes were slightly enlarged. The liver weighed 1,740 grams. The cut surfaces of the reddish-brown substance were inconspicuously mottled with numerous small dark red areas. The gall-bladder was thin-walled and contained liquid bile, and the bile passages were patent. The pancreas externally appeared normal, and on section showed the usual lobular arrangement of the evenly tan substance. The mucosa of the esophagus and stomach showed the usual postmortem changes. The smooth and unbroken mucosa of the small and large intestines presented focal regions of congestion.

The kidneys were similar in size and together weighed 365 grams. The thin capsules stripped easily, and there were several small stellate depressed regions. Both the external and cut surfaces presented many bright red round dots measuring less than 1 mm. in diameter. The cortices were of uniform width and were poorly demarcated from the light brown pyramids which showed numerous thin linear glistening white markings radiating from the apices to the bases. On the cut surface of one kidney there was a single triangular firm grayish-yellow area with its base at the cortex and apex at the pyramidal border. The smooth unbroken mucosa of the pelves was slightly elevated and markedly reddened in scattered, small, rounded regions. The ureters appeared normal. The mucosa of the urinary bladder was reddened.

The ovaries, uterus and cervix appeared grossly normal. The suprarenal glands externally appeared normal. On the cut surface there were small, poorly demarcated, red areas distributed through the usual thin peripheral band of orange cortex. The medullae were normally firm and gray. The hypophysis appeared normal.

*Microscopic Examination:* Sections of the viscera revealed partial or complete occlusion of the small blood vessels (arterioles, capillaries, and possibly venules) by rounded plugs of finely granular material which stained brightly with eosin. The diameters of the affected vessels were increased. The plugs were attached to the walls

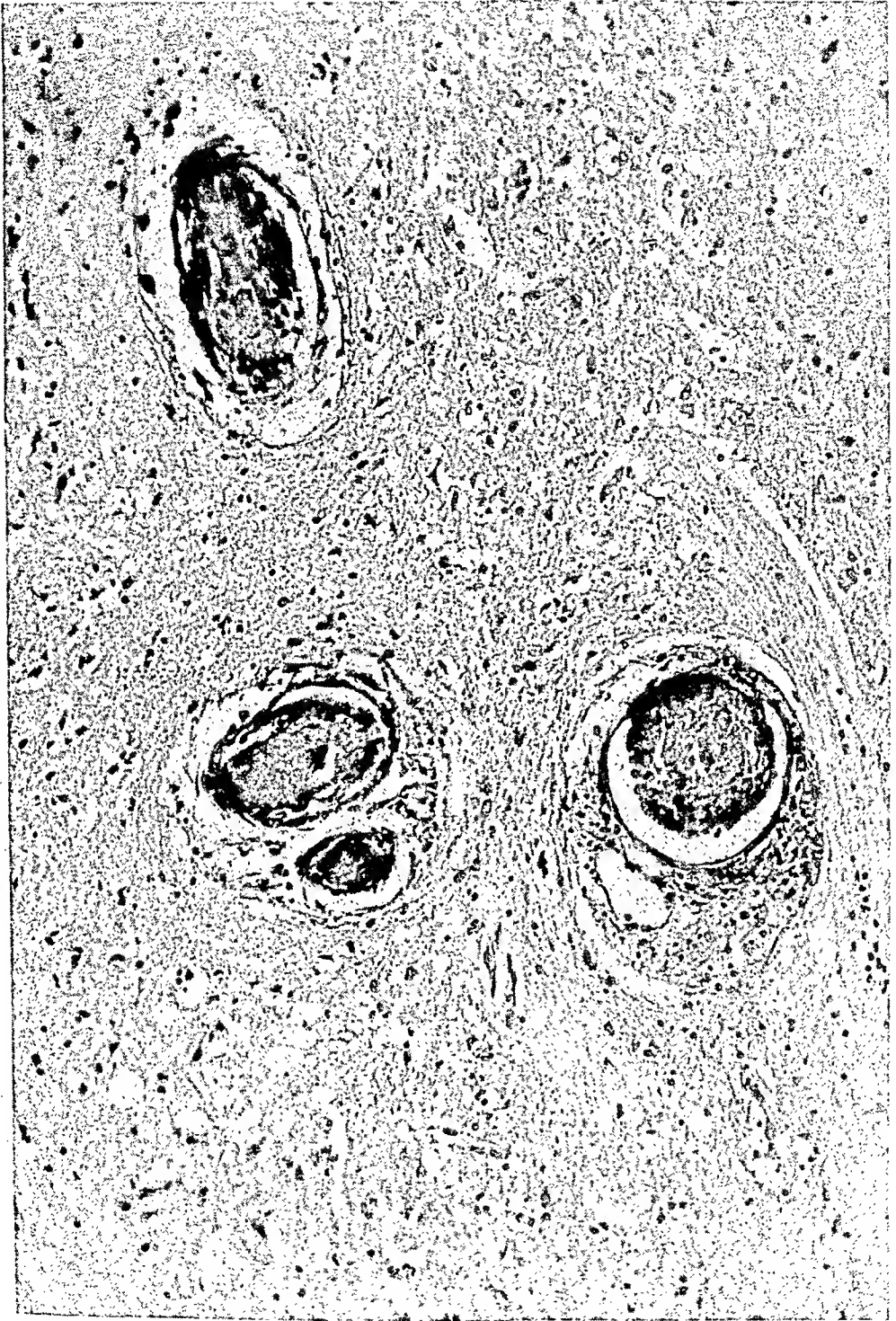


FIG. 2. Thrombotic occlusion of a large number of smaller blood vessels (veins and capillaries) of the basal ganglia. Hematoxylin eosin stain  $\times 185$ .

of the vessels along a portion of their margins. In the substance of a few of the plugs were red blood cells and nuclear debris. The endothelial cells lining these vessels were swollen and showed evidence of proliferation. Many of the plugs were partially covered with endothelium. The walls of the vessels adjacent to the site of attachment of the plugs showed degenerative changes, and in a few vessels frank necrosis. There was little inflammatory reaction in or around these vessels. Varying stages of organization of the plugs were present in a given organ, and rarely in a single vessel. These changes in the smaller vessels were particularly prominent in the sections of heart, kidneys, and adrenals, but were also present in sections of the pancreas, liver, gall-bladder, gastro-enteric tract, lungs, urinary bladder, uterus, and lymph nodes. The larger arteries and veins appeared normal.

In the heart, the vascular lesions were distributed throughout the myocardium, which in addition showed scattered miliary areas of necrosis and polynuclear leukocytic infiltration, and also regions composed of broad bands of fibrous connective tissue and small island of myocardial fibers. One auricular appendage contained a thrombus. There were bacteria-free thrombotic vegetations on the mitral valve leaflet and the subjacent tissue of the valve showed no inflammatory reaction. Several subepicardial petechiae were present.

The vascular lesions in the kidneys were more frequent in the cortices and involved the arterioles and glomerular capillaries. The basement membrane of all the glomeruli throughout the kidneys was invariably slightly thickened. Frequent subcapsular triangular regions of atrophic tubules and increased interstitial tissue infiltrated with round cells were present. There was a single ischemic cortical infarct. The tubular epithelium showed marked cloudy swelling.

In the liver the vascular lesions were found in the small vessels of the capsule and the branches of the hepatic artery in the portal spaces. There was also congestion of the sinusoids with central zone atrophy of the liver cords. The vascular lesions in the adrenals were most frequent in the subcapsular portion of the cortex. Numerous small extracapsular hemorrhages were present.

In the lungs the vascular lesions were distributed throughout the framework. There was also congestion and edema, and a single small focal area of necrosis and hemorrhage.

There was diffuse lymphocytic infiltration of the slightly increased interstitial tissue of the pancreas. The lymph nodes were congested. The vascular lesions were the only departure from normal in the gastro-enteric tract, the gall-bladder, and the uterus. The wall of the urinary bladder showed an acute inflammatory reaction with superficial ulceration of the mucosa.

*Neuropathological Examination:* The gross examination of the brain revealed multiple minute areas of softening diffusely scattered throughout the gray matter of both hemispheres. The largest lesion was found in the left occipital lobe (Area 19), measuring 1 cm. in mesio-lateral extent and 5 mm. in anteroposterior direction. The significant findings seen on horizontal cuts through the brain are illustrated in figure 1. Diffusely scattered petechial hemorrhages measuring about 1 mm. in diameter were seen in the basal ganglia on the left, in the folia of the cerebellum and in some areas of the cortical ribbon. The balance of the ventricular system appeared normal.

Survey sections were taken from several areas of the gray and white substance of both hemispheres and stained with hematoxylin-eosin, Cresyl violet, H. v. Gieson, phosphotungstic acid hematoxylin, Giemsa, and by the Loyez myelin sheath and Bodian 1 per cent protargol silver methods.

The histologic examination disclosed: (1) vascular lesions and (2) alterations of the nervous tissue proper.

(1) The vascular lesions were characterized by thrombotic occlusion of a large number of smaller blood vessels, chiefly, involving the capillaries and venules of the

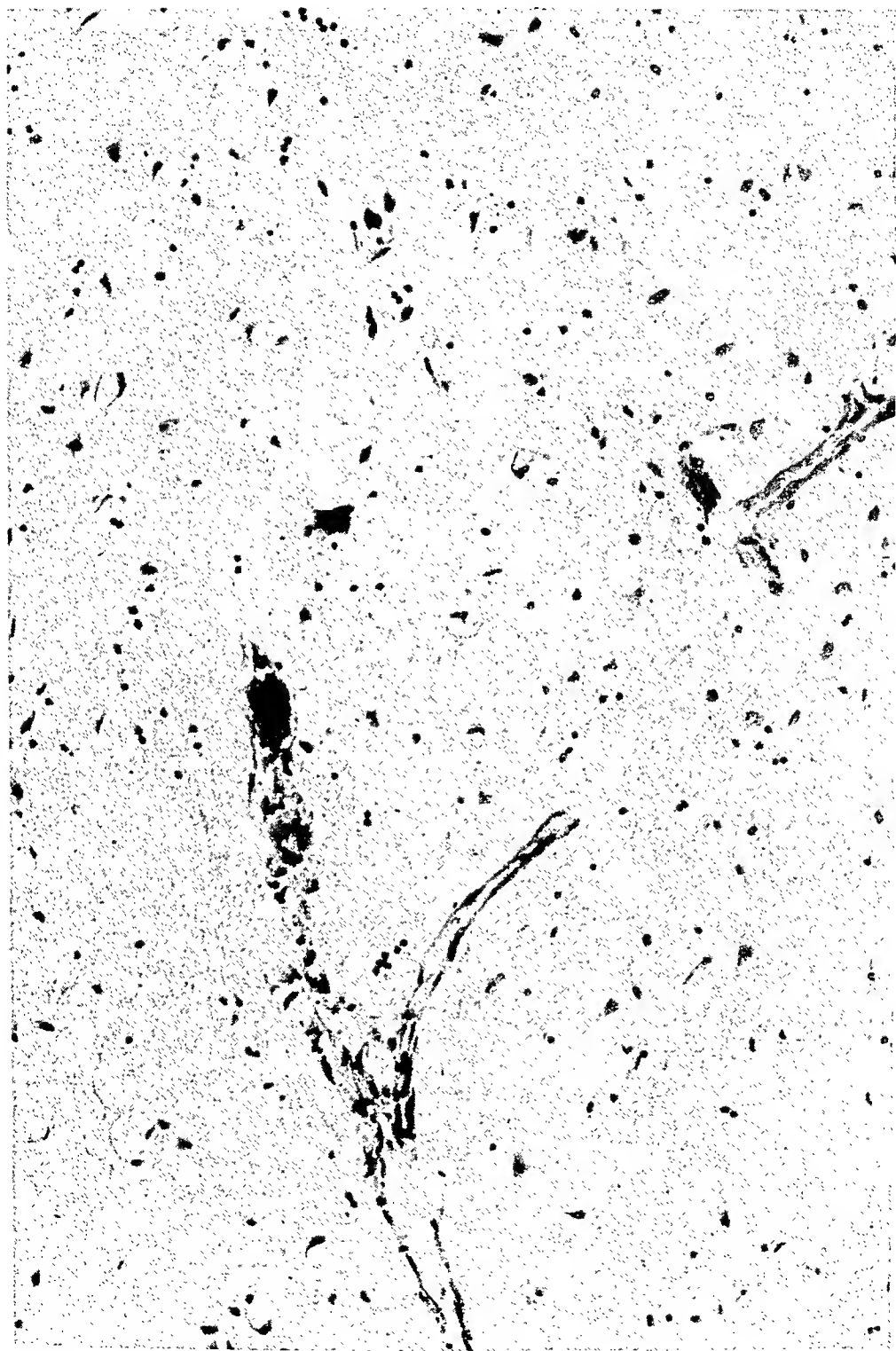


FIG. 3. Hypertrophy and proliferation of the endothelial cells of the partially thrombosed capillaries. Cresyl violet stain;  $\times 220$ .



FIG. 4. Hypertrophy and proliferation of the endothelial cells of the capillaries in absence of thrombotic occlusion. Cresyl violet stain;  $\times 260$ .

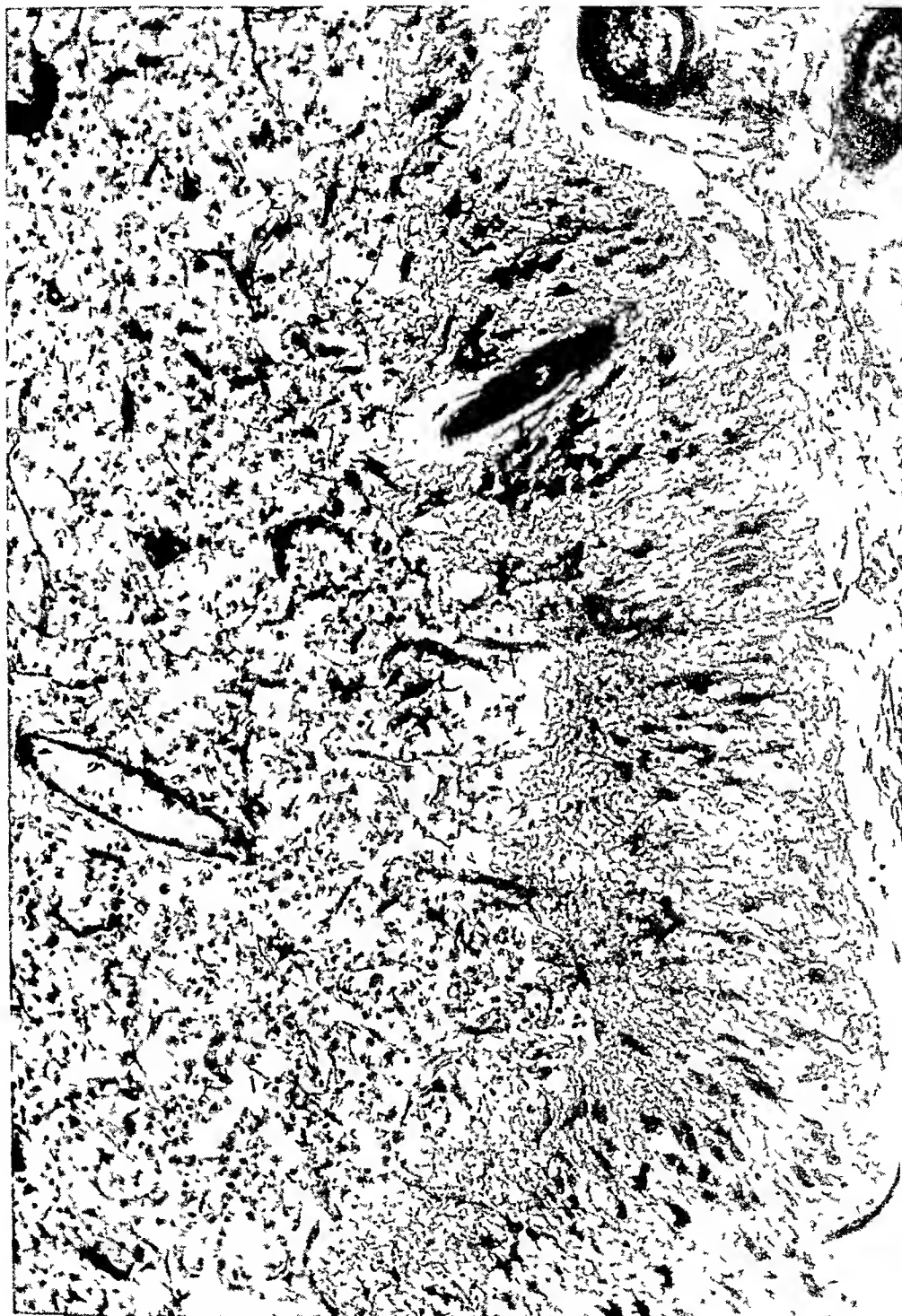


FIG. 5. Focal area of softening with large accumulation of gitter cells surrounded by an area of gliosis. Hematoxylin eosin stain;  $\times 135$ .

cortical gray matter and basal ganglia. The affected blood vessels appeared distended, their lumina were completely or partially occluded by a homogeneous or slightly granular thrombotic mass stained pinkish with hematoxylin eosin (figure 2). On closer examination it appeared that the thrombi contained only a small amount of white blood cells and very few fibrin threads. In preparations stained with Giemsa stain no platelets could be identified. The large majority of the thrombi seemed to be composed of large masses of granular debris. In sections stained with hematoxylin van Gieson the thrombotic masses were stained yellow. By means of special stains for fibrin (phosphotungstic acid hematoxylin) it was possible to demonstrate that the thrombi contained very little fibrin. Of note were the changes seen in the vessel wall. These lesions were characterized by a marked proliferation and swelling of the lining endothelium (figure 3). In some of the occluded blood vessels there were to be seen definite signs of organization of the thrombi; they appeared invaded by numerous endothelial cells and fibroblasts and were adherent to the vessel wall. In less advanced lesions the thrombi appeared only slightly attached to the vessel wall. Occasionally the lining endothelial cells showed very mild degenerative lesions and no proliferative changes. Finally, there were recent lesions in which the vessel wall of the occluded capillaries and veins appeared generally well preserved or showed only a minimal degree of endothelial proliferation. It is of interest that some of the capillaries in which there was no evidence of occlusion showed a moderate degree of proliferative and degenerative alterations of the endothelial cells (figure 4). There were no signs of an inflammatory process and no necrotic lesions of the subendothelial connective tissue present. The larger blood vessels did not disclose any pathologic changes; their lining endothelium appeared fairly well preserved.

(2) Changes in the nervous tissue proper, secondary to the circulatory disturbances, consisted of disseminated small foci of softening, characterized by a large accumulation of fat granule cells. In some of the older lesions confined to the cortical ribbon there was to be seen a layer of dense glial reaction especially marked in the overlying molecular zone of the cortex (figure 5); this contained numerous hypertrophied glial cells, mostly astrocytes with large protoplasmatic bodies and numerous processes. In many instances the small focal lesions showed more recent alterations in the form of a tissue rarefaction or early signs of anemic infarction (figure 6). And finally there were numerous scattered cortical lesions in which only a small number of nerve cells appeared degenerated and destroyed. Between these earliest lesions and those associated with glial scar formation; there were numerous transitional stages. In addition there was a small number of diffusely scattered small hemorrhages present. The leptomeninges appeared normal. No signs of an inflammatory process could be detected.

*Anatomical Diagnoses:* Acute degenerative vascular disease with thrombosis involving the small vessels, widely distributed throughout the viscera and brain; non-bacterial thrombotic mitral valvulitis; renal, pulmonary, and miliary myocardial and cerebral infarcts; myocardial fibrosis; petechial hemorrhages in the skin, pericardium, peritoneum, and renal pelves; pulmonary congestion and edema; chronic passive congestion of the liver; bilateral hydrothorax; hydropericardium; ascites; acute cystitis; slight interstitial fibrosis of the pancreas.

## DISCUSSION

The postmortem examination in this case leaves little doubt that it represents an example of the condition described originally by Moschcowitz<sup>2</sup> and by Baehr, Klemperer, and Schiffrin.<sup>1</sup> Clinically, the patient, a young girl, presented fever, thrombocytopenic purpura, hemolytic anemia, and evidence of involvement of kidneys, heart and the central nervous system. The onset was acute, following



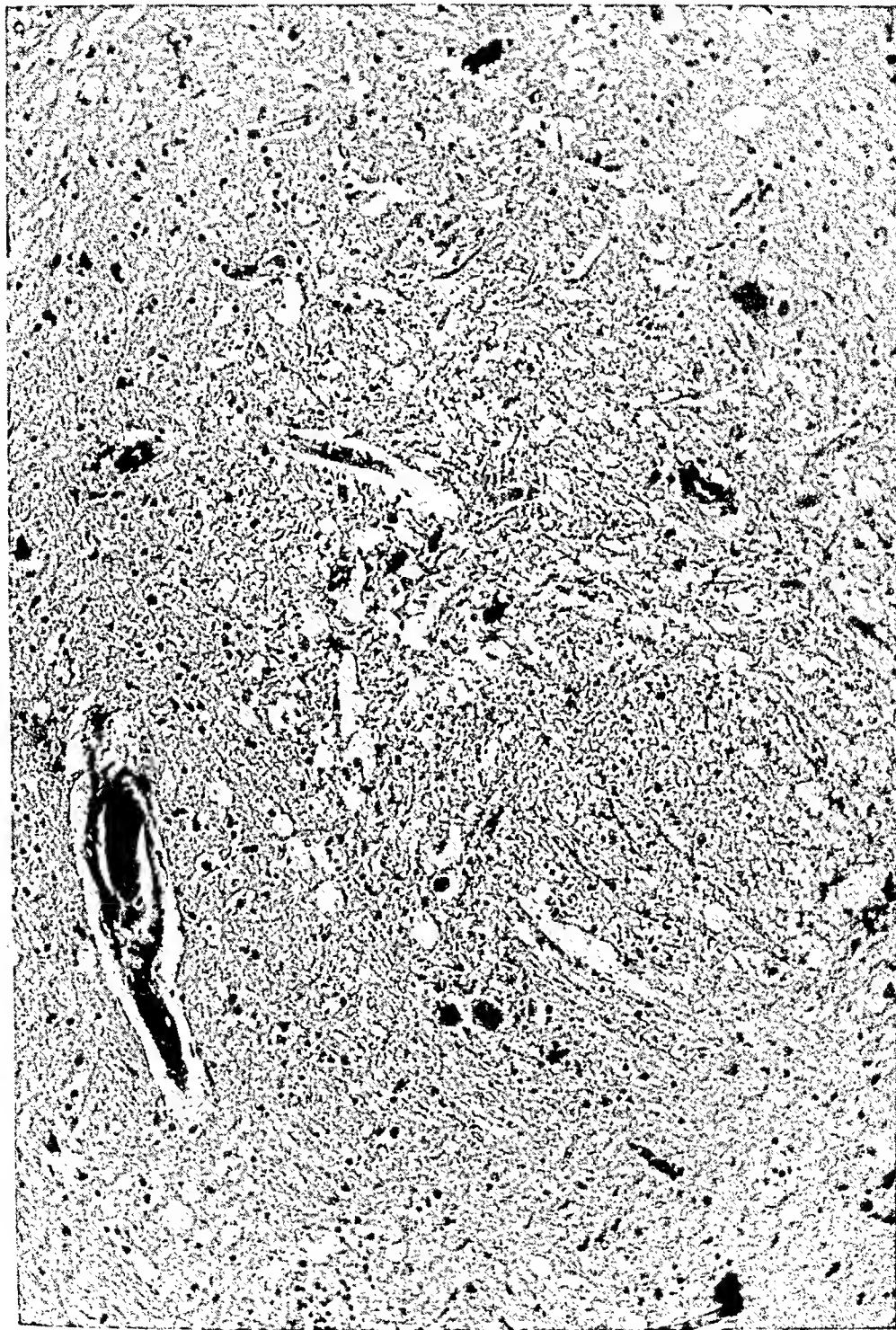


FIG. 6. Small area of recent softening characterized by tissue rarefaction and necrosis. Hematoxylin eosin;  $\times 160$ .



what may have been an upper respiratory infection, the course stormy for the first week and then followed by improvement, permitting discharge from the hospital after a six weeks' stay. However, she obviously never recovered, for in the interval between admissions she continued to have weakness, anemia, and evidences of renal and myocardial involvement. On the first admission the possibility that the illness represented a hypersensitivity to sulfonamides was considered and indeed such a sensitivity was demonstrated. However, although the patient improved after the sulfonamides were discontinued, she continued to have signs of active disease and the final exacerbation occurred without the patient having received any sulfonamide. The presence of renal, myocardial, and nervous system involvement along with the fever, thrombocytopenic purpura, and anemia suggested that this case did not fall into the usual group of thrombocytopenic purpura and the correct diagnosis was suggested. The splenectomy was obviously ill-advised, since splenectomy has not proved helpful in any of the cases reported in the literature.

The pathological findings were typical and except for the findings in the central nervous system revealed little that has not been well described in the literature. However, this patient survived longer than any of the other patients reported. For this reason many lesions showed a greater degree of organization than usual, as evidenced by the areas of fibrosis in the myocardium, the thickening of the basement membrane of glomeruli, and the dense glial reaction in the brain. In general, also, there seemed to be a greater degree of endothelial proliferation and of vessel wall change than is described in the other cases. These, too, may represent old lesions. In some instances the thrombotic plugs were covered with endothelium.

The widespread distribution of small blood vessel occlusions in the brain explains the frequency and character of the neurological manifestations of this disease. Evidence of multiple focal involvement of the brain has been the usual clinical finding. It is clear from our observations that healing with gliosis may take place.

The involvement of the heart was very extensive in this case and clinically was manifest by enlargement, gallop rhythm, dyspnea, and by persistent electrocardiographic abnormalities. The widespread distribution of areas of miliary necrosis and fibrosis indicate old and recent damage due to small vessel occlusion. Thrombotic non-bacterial endocarditis was also present in this case. Although this type of endocarditis does not usually give any physical findings, this patient developed a rather prominent murmur between her first and second admissions. This cannot be accounted for on the basis of anemia, which was severe on both admissions. In all likelihood the renal infarct and possibly the white centered fundal hemorrhages represented embolic phenomena arising from these vegetations.

We have no suggestions as to the etiology of this condition. The development of an exacerbation after what may have been an upper respiratory infection suggests some type of unusual response to infection. The patient did manifest sensitivity to sulfonamides, which may cause febrile reactions, thrombocytopenia, and hemolytic anemia, but there was no evidence that these drugs played any etiologic rôle in this case. Of the cases reported in the literature acute infection has not been a prominent preceding event. One of the cases had a sibling

who had thrombocytopenic purpura and another had a sibling who died of periarteritis nodosa.<sup>1</sup>

There is no clinical or pathological evidence at this time to suggest a relationship between this condition and Libman-Sacks disease (disseminated lupus erythematosus) in spite of the prevailing occurrence of both diseases in young women. According to Klemperer there are several unreported cases of febrile thrombocytopenic purpura among males.<sup>6</sup> Clinically Libman-Sacks disease is characterized by a more chronic and remitting course, and may include pleurisy, pericarditis, joint involvement, skin lesions, a typical verrucous endocarditis, lymph node involvement, pneumonitis, and myositis, none of which is a feature of febrile thrombocytopenic purpura. Thrombocytopenia may occur in Libman-Sacks syndrome but purpura and hemorrhagic phenomena are not presenting symptoms in that disease. Pathologically the two diseases show few similarities. The pathologic findings of Libman-Sacks disease, that is, the "wire-loop" glomerular lesions, the verrucous endocarditis, the perivascular sclerosis in the spleen, the pericardial lesions (signet-cell lesions, "hematoxylin staining bodies," the eosinophilic multinuclear coalescent bodies, and endothelial bud capillaries), and the evidences of collagen involvement,<sup>7</sup> are not seen in the acute febrile thrombocytopenic purpura. Conversely the widespread hyaline thrombotic lesions noted in this case are not a feature of Libman-Sacks disease, although occasionally thrombotic lesions are found.

#### SUMMARY

The case of a young woman with acute onset of fever, purpura, thrombocytopenia, hemolytic anemia, and evidences of renal, cardiac, and central nervous system involvement is presented. Postmortem examination revealed widespread thrombotic lesions involving arterioles, capillaries, and venules of the brain and all the viscera. The identity of this disease with that described by Moschcowitz and by Baehr, Klemperer, and Schiffrin is pointed out and the clinical and pathological features are discussed.

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## ENCEPHALOMYELORADICULITIS (GUILLAIN-BARRÉ SYNDROME) AS A COMPLICATION OF INFECTIOUS HEPATITIS \*

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DYSFUNCTION of the central nervous system has been described as one of the more serious complications of infectious hepatitis.<sup>1, 2</sup> Ordinarily the picture resembles acute alcoholism, hyperinsulinism or anoxia of the brain and is said to indicate a grave prognosis.<sup>3</sup> Symptoms suggestive of involvement of the basal ganglia have also been noted,<sup>4</sup> but no record of myelitis, radiculitis or neuritis appearing in a patient with acute hepatitis was found in a survey of the recent literature.

In 1916 a symptom complex, characterized by clinical evidence of radiculitis and "acellular hyperalbuminosis" in the spinal fluid was first described.<sup>5</sup> The name Guillain-Barré syndrome has been most commonly used to designate this picture. It has also been called infective polyneuritis, radiculitis, myeloradiculitis and "myelitis of obscure origin." When the brain stem or cerebral hemispheres are involved, the condition has been referred to as encephalomyeloradiculitis.

Grinker<sup>6</sup> states that "this syndrome of nerve, root and cord disturbance occurring separately or combined, is an acutely appearing condition arising during the course of or after a systemic infection, usually of the upper respiratory tract." Frequently there are only mild transient disturbances of motor power and sensation preceded or accompanied by root pains. On the other hand, complete paraplegia and quadraplegia may occur and with involvement of the brain stem and subsequent respiratory paralysis, death may ensue. The paralysis is of the lower motor neurone type, the sensory involvement is usually radicular in type with ill-defined "glove" and "stocking" distribution.

The syndrome attains a certain severity, remains stationary for some days, then begins to recede gradually, often over a period of many months. Deaths are not infrequent in adults, but rare in children. If death does not occur at the height of the disease, recovery is usually complete. Thus the diagnostic features of the disease are a transient myeloradiculitis with increase in the protein level but little or no change in the cell count of the spinal fluid.

The following case is described because of the uniqueness of this neurological syndrome appearing as a complication of acute hepatitis. Of further interest was the presence of an anatomical anomaly which was at first thought to explain the early neurological signs and symptoms.

### CASE REPORT

A 25 year old paratrooper sergeant was admitted to the hospital on March 20, 1945 complaining of malaise, anorexia and epigastric pain. Two days prior to entry his urine became dark and on the following day he noted jaundice. Past history was significant in that he had been ill for four weeks in 1939 with "catarrhal jaundice."

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Recovery from the previous episode of jaundice had apparently been complete, and the patient had been well since that time. Alcohol ingestion consisted of occasional moderate indulgence in beer. He had never received yellow fever vaccine.

On admission the temperature was 98.4° F., pulse 68, respirations 16. Skin and sclerae were moderately icteric. There was generalized adenopathy. The liver was 2 cm. below the right costal margin and moderately tender.

Laboratory studies showed a hemoglobin of 14.6 mg., 4.7 million red cells and 6,400 white cells per cubic mm. of blood. The urine was normal save for the presence of 12.6 mg. of urobilinogen and "two plus" bile. Icterus index was 44 and the sedimentation rate 8 mm. in one hour.

On a regimen of complete bed rest and a high protein, low fat diet, the patient showed gradual recession of the icterus and other signs and symptoms. After three weeks, the icteric index was normal and all signs of disease, save for persistent slight enlargement and tenderness of the liver and occasional temperature elevation above 99° F. had disappeared. On April 10 he began to complain of pain and numbness in the finger tips bilaterally. Supraclavicular pressure and turning of the head to the opposite side accentuated the symptoms. A roentgenographic examination of the cervical spine showed bilateral cervical ribs and it was assumed that the symptoms were due to this. During the following few days, however, pain in the calf muscles and upper back appeared. On April 16 neurological examination revealed marked hypesthesia of all modalities of the "stocking type" bilaterally to the knee, and of the "glove type" to the wrist on the right and "gauntlet type" to the elbow on the left. The patellar, achilles, bicipital, and tricipital reflexes were absent. The abdominal and cremasteric reflexes on the left were present, but exhaustible on the right. Cranial nerves at this time showed no abnormalities. On the following day the left and right lower abdominal reflexes were absent but the right upper present. On that day a left facial weakness of the lower motor neurone type was noted, and a flaccid paralysis of both arms and legs appeared. Lumbar puncture on April 17 revealed the fluid to be clear and under 200 mm. pressure. There were present 70 mg. of protein per 100 c.c. and only 4 cells (all lymphocytes) per c.c. of spinal fluid.

There was no further change in physical status for the following week, but on April 27, 1945, spinal fluid contained 192 mg. of proteins per 100 c.c. and 6 cells (lymphocytes) per c.c. of spinal fluid. At that time the facial weakness began to recede, and a slight return of muscle function in the arms was noted. Therapy consisting of passive motion and massage was instituted, and very slow but progressive return of muscle function occurred during the following month. On May 20 he was evacuated to the United States. At that time deep reflexes and voluntary contractions of all muscle groups in the arms were present, but were still absent in the lower extremities. A letter received from the patient in August 1945 stated that he was walking normally and that he had full use of his arms and legs.

#### COMMENT

The neurological and laboratory features, as well as the clinical course resulting in complete recovery satisfy the criteria of the Guillain-Barré syndrome.<sup>6</sup> This patient developed hepatitis during a large military epidemic of the disease. The clinical course of the hepatitis differed in no respect from many other mild cases until the onset of neurological symptoms.

The occurrence of other virus diseases concurrently with infectious hepatitis has received comment. Hepatitis has been shown to be caused by a filterable agent. Symptoms indicating involvement of the central nervous system, as well as autopsy confirmation of the neural lesions, have been described. The occur-

rence of a myeloradiculitis may be of significance. Whether infectious neuronitis in this case was an intercurrent disease or there was present a specific association cannot be said. The situation, however, invites speculation as both infectious neuronitis and infectious hepatitis are thought to be virus diseases. It is of interest to note the previous occurrence of hepatitis in this patient, as a possible indication of a subnormal hepatic reserve at the start of his illness. If the occurrence of myeloradiculitis in a patient with hepatitis represents a complication of the latter, rather than an intercurrent infection, the patient herein described would be one most likely to suffer such a complication.

### SUMMARY

A case of the Guillain-Barré syndrome in a patient convalescing from infectious hepatitis was presented. The possibility of the occurrence of the two diseases in the one patient representing a specific association rather than mere coincidence was discussed.

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## ALLOXAN IN THE TREATMENT OF A CASE OF ISLET CELL CARCINOMA OF THE PANCREAS WITH LIVER METASTASES \*

By LEWIS B. FLINN, M.D., F.A.C.P., EDWARD MINNICK, M.D., and  
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ORGANIC hyperinsulinism has been recognized with increasing frequency in the last few years. It is most commonly due to adenomata of the islands of Langerhans. More and more case reports appear of successful surgical removal of these tumors with consequent alleviation of symptoms. At times there seems to be a general hypersecretion of insulin by the islet cells without discernible tumor in which resection of varying amounts of pancreatic tissue has been found effective. Carcinoma of islet cells occurs much less frequently. In these cases the tumor is often slow to grow and slow to metastasize. In a few instances

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metastatic islet cell carcinoma in the liver has been found in which the metastatic tumor cells apparently produce and release insulin. One of us<sup>1</sup> reported the fifth such case in the literature up to 1941. A few more have since been reported. All have died. Brunschwig<sup>2</sup> reported such a case which was treated with alloxan.

Since Dunn, Sheehan and McLetchie<sup>3</sup> described in 1943 a selective necrosis of the islands of Langerhans of the pancreas in rabbits produced by injection of alloxan, many articles have appeared on experimental studies of the effects of this chemical. Brunschwig<sup>4</sup> has discussed the action of alloxan and Joslin<sup>5</sup> has reviewed the literature up to April, 1944. Briefly alloxan, ureide of mesoxalic acid and a component of the uric acid molecule, causes selective necrosis of the islets of Langerhans in the pancreas and of the epithelium of the convoluted tubules in the kidneys in rabbits. Initial hyperglycemia occurs, followed by hypoglycemia in a few hours and later a hyperglycemia the duration of which largely depends on the size of the dose of alloxan. Houssay,<sup>6</sup> among others, has concluded from experiments on dogs that the liver is essential for the initial hyperglycemia. Dogs have been found more sensitive than rabbits to the drug. Goldner and Gomari<sup>7</sup> found that 100 mg. per kilogram body weight of alloxan given intravenously was fatal to dogs within eight hours. A dose of 75 to 100 mg. produced uremia with death in a week. A dose of 50 to 75 mg. produced typical diabetes without renal lesions. The animals were kept alive for several weeks. On histological examination many of the beta cells were found to have disappeared from the islets, profound vacuolization of the epithelium of the pancreatic ducts had occurred and fatty changes were found in the liver. Doses of 25 mg. were without effect.

Evidence is very meagre as to the effect of alloxan on the islet cells and convoluted tubules in man. Brunschwig<sup>4</sup> administered the chemical in proportionally much larger doses than had been used in animals to several patients with carcinoma. One of these patients had an insulin-producing islet cell carcinoma. This case was repeatedly but temporarily improved clinically by the drug. For short periods hypoglycemic attacks were much less severe and much less frequent and the patient gained weight. However, in no case, even when the dose had been increased to 1 gm. per kilogram body weight, was there later any evidence of significant damage to the islet cells or epithelial cells of the convoluted tubules on histological examination.

A patient with an insulin producing islet cell carcinoma with liver metastases came under our care in August, 1945. In spite of the none too encouraging reports in the literature it seemed worthwhile to administer alloxan to this patient because the prognosis was hopeless otherwise, and because temporary relief of symptoms might occur. It is desirable to place on record the results of the administration of alloxan to another human being.

#### CASE REPORT

A 55 year old white female was admitted to the Memorial Hospital August 22, 1945. Her chief complaint was "going out like a light." For the previous six weeks she had had recurrent attacks of hypoglycemia for which her physician had prescribed four tablespoonsful of Karo corn syrup every four hours in addition to a general diet. The attacks were characterized by somnolence, hyperhidrosis, varying degrees of weakness, occasionally by maniacal tendencies and occasionally by unconsciousness requiring intravenous glucose.

Family history and past history were irrelevant except that in March, 1945 she was operated upon elsewhere because of vague abdominal symptoms and a normal appearing appendix was removed. No other pathologic condition had apparently been observed at operation.

Physical examination revealed a fairly obese woman weighing approximately 75 kilograms. She appeared apathetic, eyelids half closed, pupils equal, dilated but reacting to light and during accommodation. No significant abnormalities were evident on examination of ears, nose and pharynx. Examination of the chest revealed decreased breath sounds with dullness on percussion at the right base posteriorly. No râles were heard. The left lung was clear on percussion and auscultation. Examination of the heart revealed slight enlargement to the left and a soft blowing apical systolic murmur. The pulse rate was slightly increased. The blood pressure measured 140 mm. of Hg systolic and 60 diastolic. The abdomen was soft, obese and presented an old midline incisional scar and a recent appendectomy scar. The liver was palpable three to four fingers' breadth below the right costal margin and was nodular especially in the epigastrium. There was tenderness above the umbilicus and beneath the liver on palpation. There also, incidentally, was a congenital abnormality of the right lower extremity with absent patella and fibula, foot drop, short achilles tendon and an irregular scar over the right thigh, a result of an operation on the right femur and hip joint 37 years previously.

The urine was yellow with a specific gravity of 1.015, alkaline in reaction and there was a very slight amount of albumin. The microscopic examination was normal. The urine was not significantly different on examination throughout the patient's course in the hospital except that on one or two occasions there were from 3 to 10 red cells in the microscopic examination. Hematology report: Red blood cells 3.6 million; white blood cells 12,600; hemoglobin 10.5 gm.; color index .91; mature neutrophils 80 per cent; young neutrophils 4 per cent; lymphocytes 15 per cent; and monocytes 1 per cent. Plasma sodium chloride 460 mg. per cent, serum amylase 55 per cent of normal; blood cholesterol 193 mg. per cent.

*Course in Hospital:* Hospitalization continued for 33 days during which time there occurred a total of 60 hyperinsulin reactions, varying in degrees from slight weakness, lethargy and perspiration to actual coma. For the first five days her average carbohydrate intake was approximately 180 gm. During this time she had 13 hypoglycemic reactions, five of which were severe. The blood sugar determination ranged from 49 to 62 mg. per cent. On the sixth and seventh days the carbohydrate intake averaged 550 gm.; and there were six hypoglycemic reactions, two of them severe during this two-day period.

On the ninth hospital day an exploratory laparotomy was performed. The operative notes were as follows:

The liver presented immediately upon opening, was considerably enlarged and studded over its surface both superiorly and inferiorly with discrete nodules grossly characteristic of carcinoma. These nodules were found in both right and left lobes, had a grayish yellow appearance and varied in diameter from a few mm. to 2.5 cm. Upon exposure of the pancreas, the head and most of the body were found to be of normal appearance and consistency, but upon approaching the tail portion a tumor mass, irregular over its surface, measuring roughly 4 by 6 cm. could be seen and felt. The gross appearance of this tumor was like that noted in the metastatic nodules in the liver. This portion of the pancreas was fixed posteriorly and seemed also adherent to the spleen and splenic flexure of the colon. An enlarged lymph node was present along the foramen of Winslow but it was not hard and apparently was not involved by the process in the pancreas.

The pathological report of the biopsy of the liver was consistent with carcinoma of island of Langerhans. The day following the exploratory laparotomy the patient

had a temperature of 104 degrees. Physical signs were those of respiratory embarrassment with a decrease in breath sounds at the right base posteriorly. No râles were heard. On roentgenographic examination there was evidence of fluid in the right lower chest cavity. No atelectatic areas could be found. Penicillin was administered in dosage of 120,000 units a day for five days. On the fifth day the temperature reached normal. During this febrile period the patient had no hypoglycemic symptoms. The average carbohydrate intake from the third to the seventh postoperative day inclusive was about 100 gm. per 24 hour period. The blood sugar level on the third postoperative day was 147 mg. per cent, on the fourth 163 mg. per cent and on the seventh 60 mg. per cent. It was on the seventh day that the temperature reached normal. Thereafter increasing amounts of carbohydrate were needed. From the tenth to the thirteenth postoperative day there were 11 moderately severe hypoglycemic reactions in spite of an average daily intake of 500 gm. of carbohydrate. Seven blood sugar determinations during this period ranged from 73 to 42 mg. per cent.

On the eleventh postoperative day 5 gm. of alloxan in a 1 per cent dilution in normal saline were given intravenously taking 65 minutes for the injections. There was moderate pain and slight swelling at the site of the injection of about 12 hours' duration. No systemic reaction was apparent. No local or general reactions were noted in any later injections. Beginning three days later, on the fourteenth postoperative day, 7.5 gm. of alloxan were given slowly intravenously in a 1 per cent solution daily for four days. The next two days, the nineteenth and twentieth postoperative days, 10 gm. of alloxan were given daily as a 2 per cent solution in normal saline containing 10 per cent glucose, taking 75 and 55 minutes respectively for the injections. On the twenty-first and twenty-second postoperative days 15 gm. of alloxan were given daily as a 3 per cent solution in normal saline containing 10 per cent glucose, employing 150 and 55 minutes respectively for the injections. In other words after a trial dose of 5 gm. on the eleventh postoperative day a total of 87.25 gm. of alloxan or 1.16 gm. per kilogram of body weight were given, divided in daily doses for nine consecutive days.

Before alloxan was administered the patient had no desire for food and it was necessary to increase the amount of parenteral carbohydrate. During the nine days of alloxan therapy, the average intake of carbohydrate was about 500 gm., the supplemental carbohydrate being given partly by gavage and partly by vein. There was no appreciable clinical effect of the alloxan. Blood sugar levels varied from 37 to 165 mg. per cent without any apparent relation to carbohydrate intake or administration of alloxan. The patient's general clinical course was downward. The last day that alloxan was given 800 gm. of carbohydrate seemed to be necessary to keep her out of coma. The blood sugar readings were 45 and 41 mg. per cent. Twelve hours after this latter blood sugar determination, without additional alloxan, she seemed slightly improved and the blood sugar was 228 mg. per cent and again 12 hours later still 293 mg. per cent with an intake of 475 mg. of carbohydrate in 24 hours. The patient took fluids well during the next 12 hours then suddenly went into coma and died. Five minutes after death the blood sugar was 45 mg. per cent.

*Pathological Findings:* Liver biopsy before alloxan treatment: The specimen (figure 1) contained carcinomatous tissue the cells of which were of medium size and tended to be somewhat elongated. The cytoplasm was abundant and stained slightly red with hematoxylin and eosin. The nuclei were central, somewhat elongated, and were rich in granular chromatin. The nuclei showed a moderate degree of variation in size and shape and mitotic figures occurred frequently. The tumor cells were arranged in masses with a tendency to form rows and imperfect glands. In a few small areas, masses of tumor cells, isolated in a rather abundant connective tissue stroma, had a general resemblance to islands of Langerhans, but



the resemblance was rather superficial and special stains showed no definite alpha or beta granules. In general, the carcinomatous tissue showed much greater resemblance to pancreatic duct than to islet cell tissue.

*Autopsy* (Performed 3½ hours post mortem): The body was well developed, diffusely jaundiced, and showed evidence of recent loss of weight. Heart and lungs

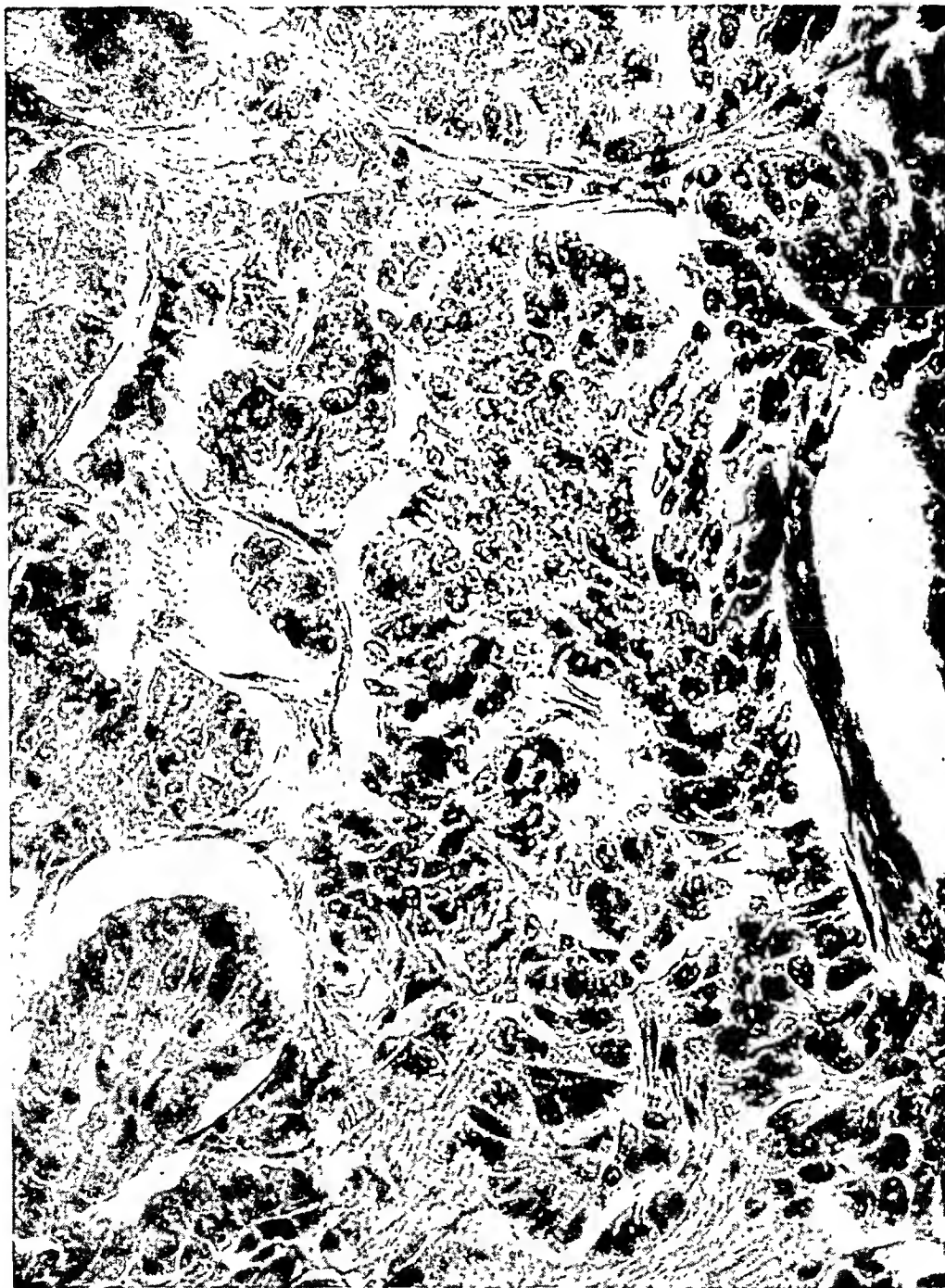


FIG. 1. Section from liver metastasis of pancreatic islet cell carcinoma. Before alloxan therapy. ( $\times 345$ .)

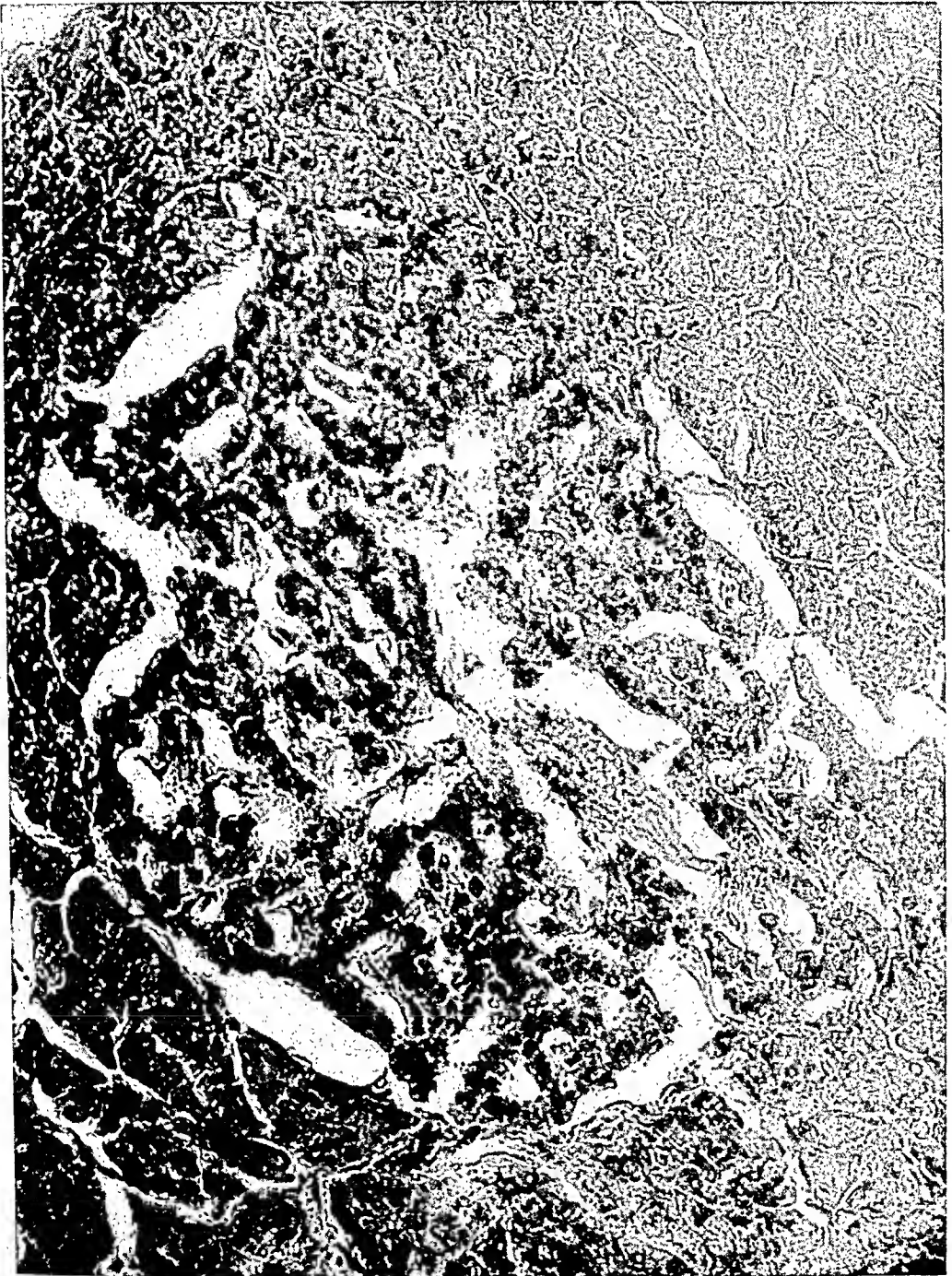


FIG. 2. Island of Langerhans after alloxan treatment, showing shrinkage. ( $\times 345$ .)

were essentially normal. Numerous fibrous peritoneal adhesions were present beneath the laparotomy scars and around the tail of the pancreas. The spleen was essentially normal. The pancreas weighed 150 grams. The distal half of the organ, including the tail and about one half of the body, was involved in a mass of firm gray tumor tissue which cut with resistance and had the general appearance of a scirrhous carcinoma. Scar tissue adjacent to the tumor extended to the spleen and cardiac

portion of the stomach. The proximal half of the pancreas and the pancreatic duct were grossly normal. The portion of the organ not involved in cancer showed very little microscopic abnormality. The cells making up the islands of Langerhans were slightly atrophied, leaving small empty spaces between the islands and their capsules (figure 2). As far as could be made out by special stains, most of the cells were beta type and extremely few were alpha type. The acinar tissue appeared entirely normal. The tumor portion of the pancreas consisted of a markedly scirrhous carcinoma made up of polyhedral cells with a slight tendency to be columnar and to form duct-like structures. This appearance was quite different from that of the tumor in the metastatic sites where there was much less connective tissue and freer growth of the tumor cells. In the pancreas, the tumor cells were of medium size and contained a moderate amount of red-staining cytoplasm. Special staining showed no differentiation into alpha and beta cells. The nuclei were centrally located, medium sized, and showed a moderate degree of variation in size and shape with occasional mitotic figures. Most of the tumor cells were arranged in rather solid masses with a slight tendency to duct formation. The stroma consisted of dense connective tissue which occasionally contained small groups of tumor cells showing a rather striking resemblance to the islands of Langerhans. These cells showed the same shrinkage as in the tumor-free portion of the pancreas. Some portions of the tumor were necrotic and infiltrated with polymorphonuclear leukocytes.

The gastric mucosa was thin, slightly congested, and atrophied. Several fibrous adhesions roughened the peritoneal surfaces of the gastrointestinal tract and the appendix was absent.

The kidneys were markedly edematous and about twice normal size. On microscopic examination the epithelium lining the convoluted tubules was granular and in many places had lost cellular and nuclear detail.

Adrenals, breasts, thyroid, parathyroid, and pituitary glands were grossly and microscopically normal.

The brain was normal.

The lymph nodes in the vicinity of the gall-bladder neck and pyloric end of the stomach and in the retroperitoneal lumbar region were enlarged up to 2 cm. in diameter. They contained carcinomatous metastases similar in appearance to the primary growth and having a rather striking resemblance to pancreatic islands.

The liver weighed 4,350 gm. and consisted quite largely of tumor. Almost the entire right lobe was replaced by firm, slightly jaundiced gray tissue which cut with resistance and had the form of nodules varying from minute size up to large conglomerate masses. The remaining liver tissue showed no evidence of cirrhosis and the gall-bladder was normal.

The microscopic findings in the liver metastases at autopsy were compared with those in the carcinomatous liver tissue obtained by biopsy. Microscopically the tumor cells in the liver (figure 3) were considerably shrunken with the cytoplasm appearing more dense and staining a darker red than in the biopsy specimen (figure 1). The nuclei were also shrunken and appeared as relatively solid masses of chromatin. The degree of variation in the nuclei was about the same as in the biopsy specimen and there was no indication that the tumor was growing any more slowly. Elsewhere, the tumor cells were necrotic and the tissue was infiltrated with polymorphonuclear leukocytes.

#### COMMENT

The cause of the hyperglycemia which occurred 24 hours before death is uncertain. In the light of animal experiments referred to above one is tempted to speculate that possibly in this patient the dose of alloxan effective on the islet

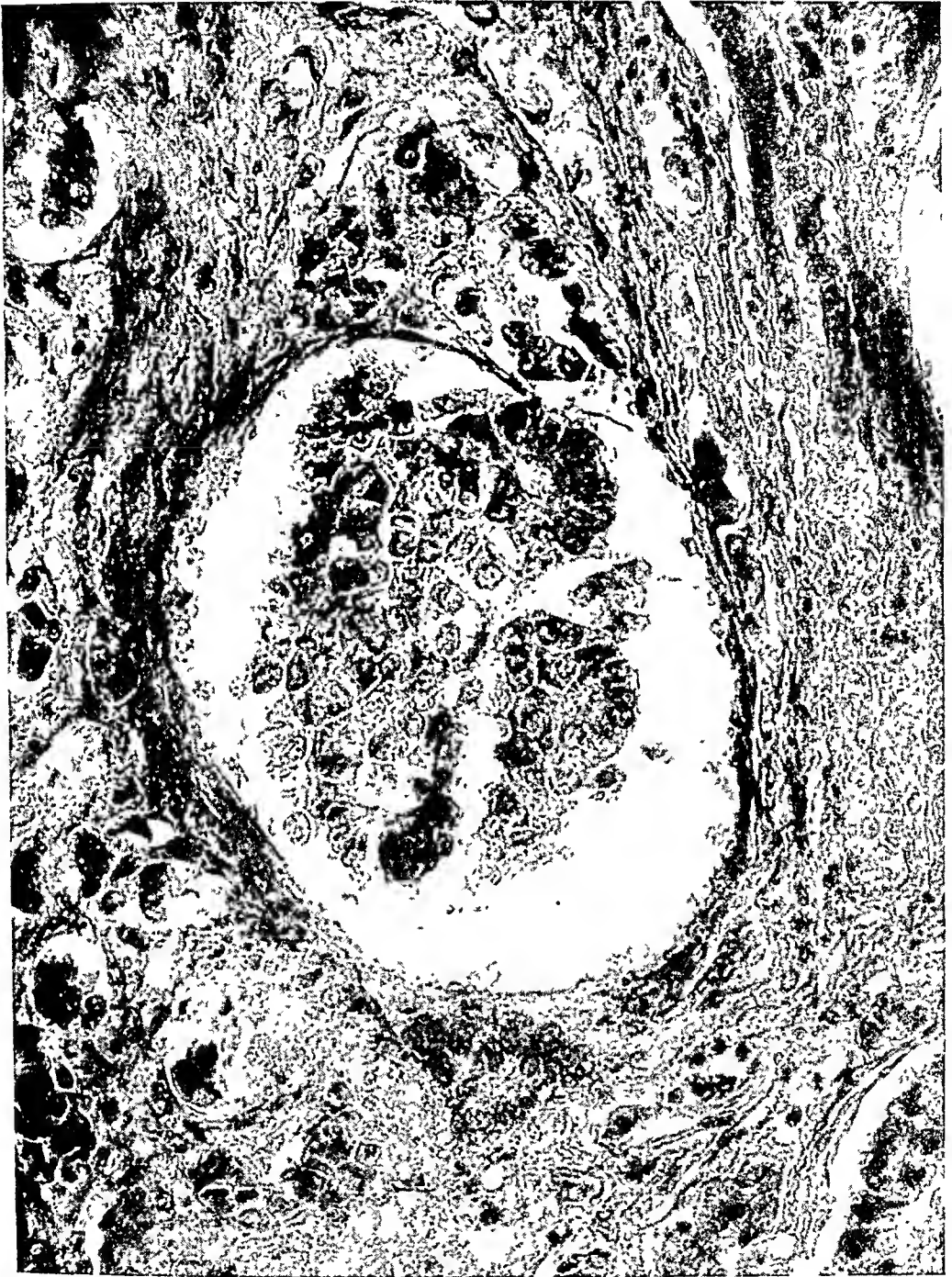


FIG. 3. Liver metastasis of pancreatic islet cell carcinoma: after alloxan therapy, showing shrinkage. ( $\times 345$ .)

cells was reached on this ninth day of treatment, the so-called initial hyperglycemia occurred followed by sudden death in the secondary hypoglycemia. Animals which survive this hypoglycemia phase go into a second and perhaps permanent hyperglycemia. Histological studies of the liver and pancreas in this patient seemed to show shrinkage of nuclei and cytoplasm in the islet cells not

invaded by the tumor and similar shrinkage of the metastatic tumor cells in the liver as compared with the biopsy obtained before alloxan was administered. No necrosis was present. This may indicate one of the earlier stages in the effect of alloxan as interpreted by animal experimentation according to several authors.<sup>8, 9, 10</sup> Five minutes after an injection of a diabetogenic dose of alloxan, slight but definite changes are discernible in the nuclei and the cytoplasm of the beta cells with a suggestion of some diminution of their specific granules. From 10 to 15 minutes after the injection there is a definite reduction of granules. These changes affect first the beta cells at the centers of the larger islets. Before the end of one hour there is some shrinkage of the affected cells which appear more closely packed and there is corresponding widening of the pericapillary spaces. In this respect the findings in this case report seem similar. By the end of one to two hours in the experimental animal definite pyknosis of nuclei is evident and at the end of three hours there is cellular separation with homogeneous eosinophilic cytoplasm. Pyknotic nuclei with an increasing amount of karyolysis and evidence of complete disintegration and disappearance of individual cells is present from five hours onward.

It was unfortunate that we were unable to determine a blood level of alloxan. Leech and Bailey<sup>8</sup> have described a method for making such determinations. In the future alloxan blood levels may be helpful in arriving at optimum dosage. It is probable that in man the effective dose of the drug will be found much higher than that heretofore used. Further knowledge of the pathological and physiological effects of alloxan should soon be forthcoming from the many studies now being conducted.

### SUMMARY

1. A case of an insulin producing islet cell carcinoma of the pancreas with liver metastases is reported with autopsy findings.
2. The patient was given alloxan intravenously for nine consecutive days with a total dosage of 1.16 gm. per kilogram of body weight.
3. No clinical effect was observed attributable to the alloxan.
4. Histological examination at autopsy revealed slight evidence of tumor cell damage in the liver metastases as compared with biopsy findings taken before alloxan therapy was begun. Some shrinking of islet cells not involved in the tumor was found. The changes noted, however, were not nearly so marked as those reported in laboratory animals and their significance therefore is not clear.

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## ACUTE FATAL POISONING FOLLOWING INGESTION OF A SOLUTION OF DDT\*

By IRVING M. REINGOLD, M.D., and IRVING I. LASKY, M.D.,  
*Los Angeles, California*

SOLUTIONS of DDT are now being widely used in the household as insecticides, and as such are definite hazards in accidental and suicidal poisoning. The amount of DDT in such solutions is of low concentration and toxicity; greater concern, however, should be given the solvents of the solutions. Neal and co-workers<sup>1, 2, 3</sup> of the National Institute of Health directed attention to the potential dangers of the solvents used in the DDT mixtures. In their reports, they showed that the ill effects in humans from the use of DDT mixtures were due to agents other than DDT in the mixtures. Recently we performed an autopsy upon a patient who swallowed approximately 150 c.c. of a solution of DDT with suicidal intent. We regard this death as a fatal poisoning due to kerosene, the solvent used in the solution, and wish to emphasize the hazards in the use of these preparations.

### CASE REPORT

*History:* The patient, a 23 year old negress, apparently in good health, and without known reason, swallowed approximately 150 c.c. of a commercial preparation of DDT. Almost immediately after the ingestion of the solution, she began vomiting; she complained of severe epigastric pain and vomited repeatedly. When she was seen by a physician, within two hours after the ingestion of the solution, she was comatose, and completely flaccid; her respirations were slow and labored, pulse slow and feeble, and pupils equally dilated. Gastric lavage produced a thick, yellow, oily, aromatic fluid which smelled like kerosene. The patient did not respond to therapy, and died within three hours after the ingestion of the solution.

*Autopsy:* The body was that of a well developed and well nourished young adult negress of the stated age of about 23 years, who weighed approximately 57 kilograms. There were no marks of external violence. The essential macroscopic pathology was found in the lungs and gastrointestinal tract. The lungs, on cut sections, disclosed

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From the Department of Pathology of the School of Medicine, University of Southern California, and the Coroner's Office of the County of Los Angeles.

edema, and irregular, dark red, firm areas of discoloration, measuring up to 3 to 4 cm. in greatest dimensions. These areas, which appeared to be recent hemorrhages, were present throughout the lungs but were more frequent in the lower lobes. The tracheo-bronchial passages were smooth and glistening. The stomach was slightly dilated and contained an oily aromatic fluid which resembled kerosene. There were several hemorrhages within the mucosa of the stomach which measured up to 2 to 3 cm. in greatest dimensions. The upper small intestine, which was markedly hyperemic, contained a large amount of the oily fluid similar to that found in the stomach. The liver and kidneys were markedly hyperemic but showed no other abnormalities. The remainder of the organs revealed no gross abnormalities. The brain and spinal cord were not examined.

The essential microscopic lesions were found in the lungs and stomach. Sections of the lungs disclosed large areas of recent hemorrhages; masses of extravasated red blood corpuscles were seen in alveoli, septums and bronchioles. These alternated with areas of edema and aerated alveoli. Sections of the stomach disclosed moderate edema of the mucosa and focal areas of recent hemorrhages. There was marked passive hyperemia of the abdominal viscera. The liver and kidneys revealed moderate cloudy swelling.

### DISCUSSION

The solution ingested contained 4 per cent of DDT, 4 per cent of "lethane," and 92 per cent of refined petroleum oil (kerosene). From the lesions observed at autopsy, and from the formula of the solution, kerosene, and not DDT, was considered to be the etiological agent of the fatal poisoning.

According to Deichmann, Kitzmiller, Witherup, and Johansmann,<sup>4</sup> in fatal cases of kerosene poisoning, death usually occurs in two to 20 hours. The fatal outcome is the result of the absorption of the kerosene from the gastrointestinal tract and its passage by way of the blood stream to the organs and tissues of the body, notably the lungs. The kerosene may be aspirated into the tracheo-bronchial tree. It is capable of producing severe corrosive lesions accompanied by local exudative inflammatory changes. Following the absorption there is evidence of generalized toxemia and depressant effects on the central nervous system. The most important changes, however, occur in the lungs, which disclose vascular and parenchymatous damage.

The chief histopathological findings in animals exposed to high concentrations of DDT, according to the investigators of the National Institute of Health,<sup>5, 6</sup> are moderate degenerative changes of the liver. In no organs are sufficient pathological changes found to account for the death of the animals. When given in sufficiently large doses, and usually over a long period of time, DDT may cause definite signs of poisoning, always preceded by indications of injury to the liver and kidneys.

It is unlikely that "lethane," the trade name for the aliphatic thiocyanate used in the preparation as a supplementary insecticide, was of any significance in causing the fatal poisoning. The oral lethal dose of "lethane" ranges from 0.05 c.c. to 0.14 c.c. per 100 grams of body weight—in dogs and rats, respectively.<sup>7</sup>

The sudden death (within three hours) and pathological findings in this case indicate acute poisoning due to the kerosene. The large areas of pulmonary hemorrhages and edema are seen in kerosene poisoning. Besides, there were no areas of necrosis or fatty degeneration of the liver or kidneys as are described in experimental poisoning with DDT. In addition, it is probable that the amount

of DDT in the ingested solution was not sufficient to cause fatal poisoning. The acute toxicity of DDT given orally to the experimental animal is not of a high order. For instance, the oral median lethal dose for white rats ranges from 200 to 300 mg. per kilogram of body weight, for rabbits about 500, for dogs about 200, and for mice about 400.<sup>8</sup>

Apparently the pulmonary changes were brought about by absorption of the kerosene from the gastrointestinal tract and its subsequent excretion into the lungs, and not by the aspiration of the kerosene into the respiratory tract.<sup>9</sup>

The danger of poisoning from kerosene and other petroleum oil solvents used in solutions of DDT could be eliminated by using water-suspensions of DDT. Furthermore, the apparently low toxicity of DDT in such mixtures would exclude it as a hazard in acute poisoning.

### CONCLUSIONS

1. Acute fatal poisoning followed the ingestion of a solution of DDT. The poisoning is considered to be due to kerosene, the solvent used in the solution.
2. The essential pathological findings were severe pulmonary hemorrhages and edema, gastric hemorrhages, and the presence of kerosene in the upper gastrointestinal tract.
3. The wide use of kerosene solutions of DDT as insecticides make them potential dangers in accidental and suicidal poisoning.

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## EDITORIAL

### *PREFRONTAL LOBOTOMY FOR THE RELIEF OF UNBEARABLE PAIN*

RELIEF of pain has ever been one of the cardinal functions of the physician. To this end possibly more time and energy have been devoted than to any of the other variegated healing practices, with the result that great strides have been taken toward perfecting anesthesia and analgesia as well as mechanical and surgical procedures for alleviating pain. Among the neurosurgical procedures that have been employed in the past may be listed alcohol injection of peripheral nerves, nerve section, sympathectomy, vagotomy, and chordotomy with division of the pain tracts in the spinal cord. Nevertheless, certain instances of intractable pain have defied all efforts of surgeons, physicians, and drug chemists to furnish complete and lasting relief. The miserable victims of such unbearable pain almost inevitably end up as drug addicts or suicides. It was in an attempt to fill the breach in our therapeutic armamentarium created by this group of unfortunate individuals that Watts and Freeman<sup>1</sup> resorted to a more radical, yet more subtle neurosurgical approach to the problem, namely psychosurgery in the form of prefrontal lobotomy.

Psychosurgery of this type was originally introduced as a method of treating certain grave psychotic states. Stimulated by the results of surgical treatment of mental disorders initiated by Moniz over a decade ago, Freeman and Watts<sup>2</sup> began to perform prefrontal lobotomies on patients with various types of psychoses. Early in their work they were impressed with the subtle change that took place in patients thus operated upon. These patients continued to manifest their same hallucinations and delusions, but were no longer bothered by them. Anxiety and fear were relieved, panic states no longer occurred, and obsessive thinking disappeared. It was the emotional reaction to the ideas that had disappeared. When this fact was more fully investigated, it was realized that the incisions in the frontal lobes interrupted the anterior thalamic radiation. Freeman and Watts believe that the frontal lobes subserve the functions of foresight and insight, particularly as related to the self, and that it is in relation to these ego functions that the affective coloring supplied by the thalamus is of overwhelming importance for the adjustment of the individual in his social milieu.

The operative mortality was only 3 per cent, but, although the results of prefrontal lobotomy were highly gratifying in a reasonably large percentage of the 260 psychotic patients followed from six months to nine years after operation, the authors frankly admit that the patients were far from

<sup>1</sup> WATTS, J. W., and FREEMAN, W.: Psychosurgery for the relief of unbearable pain, *Jr. Internat. Coll. Surg.*, 1946, ix, 679.

<sup>2</sup> FREEMAN, W., and WATTS, J. W.: Prefrontal lobotomy: survey of 331 cases, *Am. Jr. Med. Sci.*, 1946, ccxi, 1.

healthy, particularly at first. In undergoing this operation they had exchanged one form of abnormal behavior for another. Whereas during the psychosis they had been too preoccupied with themselves, following operation they were at the mercy of every passing external stimulus. The emotional intensity characteristic of the psychosis gave way to the emotional shallowness of the postoperative state, and the imaginative activity which had been at its height during the psychosis underwent more or less permanent reduction.

Patients who made a satisfactory recovery were, however, far from inanimate clods. They were for the most part cheerful, friendly, uncomplicating, outspoken, and buoyant. They fell in with the mood of their companions, were quick to follow suggestions and were not embarrassed, glum or self-conscious. They took an active interest in everything that went on about them, read the papers, attended movies, worked regularly and played games with intelligence and foresight. With them the emotional component of foresight and insight was sufficient for meeting external situations of moderate complexity. It seemed, however, that introversial preoccupation was no longer possible. If asked about themselves and their previous troubles, they might recall various ideas or particular episodes, but without concern, and many patients had a more or less complete amnesia for the whole psychotic period.

Among the 360 patients with nervous and mental disorders upon whom Watts and Freeman performed lobotomies were a number who complained of unbearable pain. Their complaints of pain appeared excessive and out of proportion to the painfulness of the condition itself. Following lobotomy, there was not only a disappearance of the anxiety, apprehension, and nervous tension, but the incessant complaints of pain were no longer heard. These observations led the authors to employ psychosurgery for relief of pain in selected cases of radiculitis, carcinoma, and tabes dorsalis. The individuals were known to be in great pain and yet the fear of pain seemed to be an equally important factor. In this group of patients the complaints about pain also ceased after prefrontal lobotomy and it was possible to reduce or discontinue entirely the use of narcotics. Although the complaining ceased and the patients no longer requested hypodermics and appeared comfortable and in good spirits, when asked directly about pain, some admitted it was still present. In fact, they stated that the pain was exactly as it was before the lobotomy. Apparently psychosurgery alters the individual's reaction to pain without materially changing his ability to feel pain. Perception of pain is still present, but the psychological reaction to pain is changed. Pain may be present, but when it no longer raises a mental picture of future disability or death and what this may mean to one's family, it can then be borne with equanimity.

This entire concept of affording relief from unbearable pain by altering the victim's reaction to pain is indeed a fascinating one. To be sure, pre-

frontal lobotomy is a drastic and radical procedure, to which we should resort only in carefully selected instances after more conservative measures have failed to afford relief. However, it may prove to have a very real place in the therapy of severe tabetic crises, metastatic malignancy, and other conditions characterized by excruciating pain, either persistent or paroxysmal.

W. H. B.

## REVIEWS

*A Primer of Electrocardiography.* By GEORGE BURCH, M.D., F.A.C.P., Associate Professor of Medicine, Tulane University School of Medicine; Senior Visiting Physician, Charity Hospital; Consultant in Cardiovascular Diseases, Ochsner Clinic; and TRAVIS WINSOR, M.D., Instructor in Medicine, Tulane University School of Medicine; Assistant Visiting Physician, Charity Hospital, New Orleans. 215 pages; 24 × 15 cm. 1946. Lea & Febiger, Philadelphia. Price, \$3.50.

This small volume is intended for the beginner in electrocardiography. It is profusely illustrated by diagrams only. Controversial questions are avoided. The tone is rather didactic. Theory is adequately covered. It is recommended to the medical student and to the beginner in electrocardiography.

W. J. L.

*Diseases of the Retina.* By HERMAN ELWYN, M.D., Sr. Assistant Surgeon, New York Eye & Ear Infirmary. 587 pages; 23.5 × 16 cm. 1946. The Blakiston Company, Philadelphia. Price, \$10.00.

The presentation of the material is systematic and thorough, the book being divided into eight parts under which all retinal diseases are classified. There is ample discussion of the diagnosis, pathology, and treatment of all the commoner diseases, and most of the rarer retinal conditions. The association of retinal vascular disease with systemic disease is adequately emphasized and this section should be of great value to ophthalmologists and internists alike.

The illustrations in this volume have been collected from many sources. They aptly illustrate many conditions. In a work of this character, however, one might have expected to find more original drawings or photographs from the author's clinical practice.

The clarity of expression and the systematic presentation of the subject more than offset any adverse comment. There is no doubt that such a modern text on the retina will fill a much needed vacancy in our ophthalmic literature.

F. E. K., JR.

*Treponematoses.* By ELLIS H. HUDSON, M.D., D.T.M. & H.; Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D. ScD., F.A.C.P., F.R.C.P. 122 pages; 24 × 16 cm. 1946. Oxford University Press, New York. Price, \$2.50.

In this analytical history of treponematoses the author furnishes a convincing explanation of the development of syphilis. His analysis of the debated relationship of the discovery of America by Columbus and the spread of syphilis in Europe is of great interest. The discussion of the autogenic and clinical relationship between yaws and syphilis is expertly handled. Classification, clinical features, pathology and epidemiology of diseases caused by the treponemas are presented in scholarly fashion.

T. E. W.

## BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

- Recent Advances in Clinical Pathology.* By various authors. Edited by S. C. DYKE, D. M. (Oxon), F.R.C.P. (London). 468 pages; 21 × 14 cm. 1947. The Blakiston Company, Philadelphia. Price, \$5.50.
- Experiences with Folic Acid.* By TOM D. SPIES, M.D. 110 pages; 24 × 15.5 cm. 1947. The Year Book Publishers, Inc., Chicago. Price, \$3.75.
- Clinical Pediatrics.* Oxford Medical Outline Series. By I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D. 409 pages; 22 × 14.5 cm. 1947. Oxford University Press, New York. Price, \$4.00.
- Pharmacopoeia of the United States.* Thirteenth Edition. By authority of the United States Pharmacopoeial Convention. 956 pages; 23.5 × 16 cm. 1947. Mack Publishing Company, Easton, Pa. Price, \$8.00.
- The Development of Inhalation Anaesthesia* (with special reference to the years 1846-1900.) By BARBARA M. DUNCUM, Nuffield Department of Anesthetics, University of Oxford. 640 pages; 23 × 14.5 cm. 1947. Oxford University Press, New York. Price, \$12.00.
- Mental Mischiefs and Emotional Conflicts.* Psychiatry and Psychology in Plain English. By WILLIAM S. SADLER, M.D., F.A.P.A., Chicago. 396 pages; 24 × 16 cm. 1947. C. V. Mosby Company, St. Louis. Price, \$6.00.
- Maladies et Syndromes Rares Ou Peu Connus.* Description Clinique-Repertoire des Signes et Liste des Noms Propres. By A. AIMES, Professeur à la Faculté de Médecine de Montpellier. 208 pages; 23 × 15.5 cm. 1946. Masson et Cie, Paris.
- La Réticulose Histiomonocytaire.* By P. CAZAL, Chef de Clinique à la Faculté de Médecine de Montpellier. 196 pages; 25.5 × 16.5 cm. 1946. Masson et Cie, Paris.
- Education for Responsible Living.* Third Printing. By WALLACE B. DONHAM, LL.D., L.H.D. 309 pages; 22 × 14.5 cm. 1946. Harvard University Press, Cambridge, Mass. Price, \$3.00.
- Dr. Samuel Guthrie, Discoverer of Chloroform.* By JESSE RANDOLPH PAWLING, M.D., M.A., F.A.C.P. 123 pages; 22.5 × 14.5 cm. 1947. Brewster Press, Watertown, N. Y. Price, \$3.50.
- Allergy in Theory and Practice.* By ROBERT A. COOKE, M.D., Sc.D., F.A.C.P., Director Dept. of Allergy, Roosevelt Hospital, N. Y. C. 572 pages; 24 × 16 cm. 1947. W. B. Saunders Company, Philadelphia. Price, \$8.00.

# COLLEGE NEWS NOTES

## ADDITIONAL LIFE MEMBERS

The College is gratified to announce that, under date of May 7, 1947, the following Fellows became Life Members of the College:

Barnett Greenhouse, New Haven, Conn.  
Standiford Helm, Evanston, Ill.

## REGISTRATION STATISTICS

### TWENTY-EIGHTH ANNUAL SESSION

CHICAGO, APRIL 28-MAY 2

The registration at the Twenty-eighth Annual Session was the largest that the College has ever had. The registration figures, tabulated according to categories of attendants, are given below. It is interesting to note that the number of persons attending was more than double that of the last Annual Session held in Chicago, which was in 1934. The extraordinary program of entertainment, which was prepared by the Ladies Committee, is believed to be responsible for the large increase of attendance by wives of registrants. The reason for the rather surprising drop in the number of students who attended the Morning Lectures and General Sessions has not been ascertained.

	Members	Guest Physicians	Guest Non-Physicians	Students	Exhibitors	Ladies	Total
CHICAGO (1947)	1694	1382	70	137	518	609	4410
PHILADELPHIA (1946)	1539	1129	23	485	503	358	4037
ST. PAUL (1942)	827	541	43	75	200	162	1848
CHICAGO (1934)	690	660		420	194	121	2085

## THE ASSOCIATION OF AMERICAN PHYSICIANS 60TH ANNUAL MEETING

The 60th Annual Meeting of the Association of American Physicians was held at Atlantic City, New Jersey, during the first week of May, 1947. Dr. A. H. Gordon, of Montreal, was elected President, succeeding Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia; Dr. Francis G. Blake, F.A.C.P., New Haven, was elected Vice-President; Dr. Walter Bauer, F.A.C.P., Boston, Treasurer; Dr. Cecil J. Watson, F.A.C.P., Minneapolis, Recorder; and Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, Secretary. Dr. Joseph T. Wearn, F.A.C.P., Cleveland, heretofore Secretary, was elected a Councilor. Dr. Eugene F. Dubois, F.A.C.P., of Cornell University Medical School, New York City, was awarded the George M. Kober Medal for "marked contributions to medicine during his career."

## GENERAL KIRK TO RETIRE AS ARMY SURGEON GENERAL

On the expiration, May 31, 1947, of the term of Major General Norman T. Kirk, F.A.C.P., as Surgeon General of the U. S. Army, he will be succeeded in that office by Brigadier General Raymond W. Bliss. Dr. Bliss graduated from the Tufts College

Medical School in 1910. He entered the Army shortly thereafter and has served with distinction through both World Wars. Dr. Bliss did postgraduate work at the Army Medical School and, in surgery, at the Harvard Medical School. Since January, 1946, he has held the position of Deputy Surgeon General.

Brigadier General George E. Armstrong has been nominated to succeed General Bliss as Deputy Surgeon General. Dr. Armstrong graduated from the University of Indiana Medical School and was commissioned in the Army in 1926. Since June of last year, he has been Chief of the Personnel Division of the Surgeon General's office.

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### GENERAL PRACTICE IN HOSPITALS

The following resolution, which was passed by the House of Delegates of the American Medical Association last December, is thought to be of sufficient interest to readers of the ANNALS OF INTERNAL MEDICINE to be reprinted here in full.

"WHEREAS, The House of Delegates of the American Medical Association has established an individual section on the general practice of medicine; and

"WHEREAS, The general practitioner has been recognized as a separate branch in the medical profession; and

"WHEREAS, This group has shown its interest in this section by registering 939 members in the section at the 1946 American Medical Association meeting in San Francisco; and

"WHEREAS, Their scientific section meetings were well attended; and

"WHEREAS, The House of Delegates has already voiced its approval of such sections in the separate state and county societies that are component parts of the American Medical Association; and

"WHEREAS, Sections on general practice have been started in some recognized hospitals that are approved by the American College of Surgeons and the Council on Medical Education and Hospitals and have been accepted by those bodies; and

"WHEREAS, Many hospitals have not established general practice sections in their visiting active staffs and their governing heads are doubtful whether such action has the approval of the bodies which set up the rules and regulations for the approval of their hospitals for interns and residents; therefore be it

"RESOLVED, That hospitals should be encouraged to establish general practitioner services. Appointment to a general practice section shall be made by the hospital authorities on the merits and training of the physician. Such a general practice section shall not per se prevent approval of a hospital for the training of interns and for residencies. The criterion of whether a physician may be a member of a hospital staff should not be dependent on certification by the various specialty boards or membership in special societies."

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Colonel Robert H. Lowry, (MC) USA, F.A.C.P., Washington, D. C., has been awarded the Legion of Merit for his distinguished services as Commanding Officer of the General Dispensary, and as Surgeon of the Military District of Washington, February, 1943, to August, 1946.

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Commander Paul H. Morton, (MC), USN (Associate) Parris Island, S. C., has been awarded the Air Medal for his valuable activities in improving the physical and mental standards of our Naval aviators who were charged with protecting our supply lines in the English Channel during the last war.

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Dr. Francis E. McDonough, F.A.C.P., Boston, Mass, is a recipient of the Legion of Merit. As a medical officer in the A.U.S., Dr. McDonough had the responsibility

of safeguarding the health of bomber command personnel in India and China. This award was made in recognition of the unusual success which he had in performing this duty.

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Dr. Ward A. Darley, Jr., Denver, College Governor for Colorado, has been appointed Director of the University of Colorado Medical Center, which includes the University's Schools of Medicine and Nursing, as well as the Colorado General Hospital and the Colorado Psychopathic Hospital.

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Dr. Leon Unger, F.A.C.P., Chicago, was installed as President at the recent meeting of the American College of Allergists. At this meeting Dr. Hal McCluney Davison, F.A.C.P., Atlanta, Ga., was elected to the position of President-Elect.

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Dr. F. William Sunderman, F.A.C.P., Philadelphia, Pa., has been elected Vice President of the American Board of Pathology.

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Dr. John W. Ferree, F.A.C.P., New York, N. Y., has been appointed Associate Executive Director of the National Health Council, New York. Dr. Ferree was formerly a division director of the American Social Hygiene Association. He is a graduate of the University of Indiana Medical School, and has been engaged in public health work since 1936.

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Dr. Howard F. West, F.A.C.P., Los Angeles, President of the American Heart Association, has announced the appointment of Dr. Charles A. R. Connor (Associate), New York, as Associate Medical Director. Dr. Connor, a graduate of the New York University College of Medicine, is affiliated with the teaching staff of that school and also holds appointment as Assistant Chief of the Cardiovascular Clinic in the Lenox Hill Hospital and as Attending Consultant to the Veterans Administration. Dr. Connor will assist the Association's Medical Director in the task of stimulating research and the dissemination of information concerning diseases of the heart and circulation.

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The College wishes to express its gratitude to Dr. J. R. Pawling, F.A.C.P., Watertown, N. Y., for his kindness in sending to the College Library of Publications by Members a copy of his book entitled, "Dr. Samuel Guthrie, Discoverer of Chloroform," published by the Brewster Press, Watertown, N. Y., 1947.

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Dr. Franklin C. Cassidy, F.A.C.P., formerly Manager of the Veterans Administration Hospital, Outwood, Ky., has recently been assigned to the position of Manager at the Veterans Administration Hospital, located at 1025 Lamar Avenue, Memphis, Tenn. This hospital is in process of being converted from the care of general medical and surgical patients to an institution devoted exclusively to the care of the tuberculous.

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#### RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to May 13, 1947, inclusive).

Charles L. Anderson, Jackson Heights, N. Y. (Lt. Col., MC, AUS)

Mackinnon Ellis, Bryn Mawr, Pa. (Comdr., MC, USNR)

Robert C. Manchester, Norfolk, Va. (Comdr., MC, USNR)

Joseph D. Landry, New Orleans, La. (Capt. MC, AUS)

Richard M. Nay, Rochester, Minn. (Major, MC, AUS)



*OBITUARY*

## DR. MARK ATKINS BROWN

Mark Atkins Brown, M.D., F.A.C.P., was born in Cincinnati, Ohio, on October 19, 1874, and died January 13, 1947, at the Christian R. Holmes Hospital of cerebral hemorrhage.

Dr. Brown studied at the University of Cincinnati College of Medicine, receiving his M.D. degree in 1894. His long career as an outstanding internist and teacher in Cincinnati is marked by the following appointments: Professor of Materia Medica and Therapeutics, Cincinnati College of Medicine and Surgery, 1897-1898; Professor of Physical Diagnosis, Miami Medical College, 1898-1901; Attending Physician, Cincinnati General Hospital, 1901-1918; Assistant Director, 1918-1931; Professor of Medicine, University of Cincinnati College of Medicine and Surgery, 1901-1931.

Mark Brown was a member of the Academy of Medicine of Cincinnati and the Ohio State Medical Association; a Fellow of the American Medical Association, and, since 1931, of the American College of Physicians.

It is noteworthy that in the thirty years during which Dr. Brown was Professor of Medicine, the College of Medicine grew and developed as a University unit, in great part due to the influence of his high competence and unstinted devotion. It is characteristic of his great heart and his loyalty to the institution that, in his will, he named the University as beneficiary to receive, after the death of his widow, one-half of his estate, the income to be used for the benefit of the department in which he had served. Thus the good that Dr. Mark Brown did in his lifetime will continue perpetually.

M. A. BLANKENHORN, M.D., F.A.C.P.,  
Governor for Ohio

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